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## THE RADIUM DEPARTMENT OF ST. BARTHOLOMEW'S HOSPITAL, LONDON

by

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The radium supplies of the hospital are administered by a committee, called the Cancer Research Committee, appointed jointly by the hospital and its medical college. Under the aegis of this committee, investigations into the biological effects of the radiations from radioactive substances and the treatment, under research conditions, of patients suffering from cancer are carried out in the laboratories, wards and special departments of the college and hospital.

It will be seen that research and treatment are not confined to one department, but so distributed that various groups of workers may concentrate their efforts on different specific problems.

No treatment of any kind is given in the radium department, the main functions of the department being the maintenance of an efficient radium service and the preservation of the radium from loss or damage.

This note is confined to the organisation and equipment devoted to these purposes.

### Amount of Radium and its Distribution

Although within a few weeks the total amount of Radium element at the disposal of the Cancer Research Committee will be in excess of one and a half grammes, the amount at present in use is only eleven hundred milligrammes.

Half of this quantity is distributed in the form of Radium Sulphate amongst two hundred and fifty containers — chiefly platinum needles.

Another half gramme, in the form of a solution of Radium Bromide in distilled water, is used for the production of Radium Emanation (Radon).

(The remaining half gramme which is now on order will be contained in platinum needles and tubes; this will bring up the total number of containers filled with insoluble salt to approximately 500.)

The smallest needles have each a content of  $\frac{1}{3}$  mg. Ra. element and the two largest single containers of 50 mg. In all cases, for cancer treatment, the filtration is never less than 0.5 mm. of platinum, and may amount to 2 mm. of platinum.

The final distribution of the whole supply as arranged at present will be as follows:

Needle Content in Mg. Ra. El.	0.33	0.5	1.0	1.5	2.0	3.0	5.0
No. of Needles . . . . .	20	92	90	22	163	82	13

Two tubes of 50 mg., 11 tubes of 10 mg., all in platinum.

Three plaques in Monel Metal of 2.5, 5 and 10 mg. respectively.

In solution, 510 mg.

### Housing and Equipment

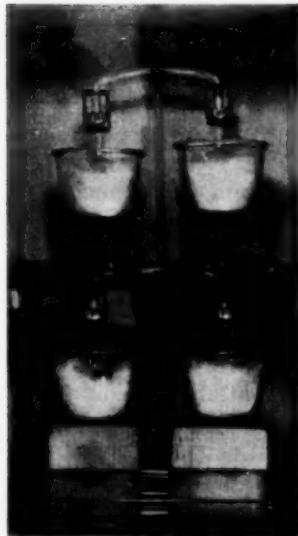


Fig. 1. Showing the distribution of radium solution amongst 4 flasks.

The scheme for the rebuilding of certain parts of the hospital within the next two or three years, includes the provision of permanent quarters for the radium department at the top floor junction of the medical and surgical in-patient blocks. Pending this consummation, the temporary quarters consist of six rooms in the out-patient department. One room is used mainly for clerical purposes, — dealing with requisitions, records etc., another as a combined laboratory and workshop, and a third for housing the apparatus used for extracting the radon from solution, purifying it and filling it into special appliances. The remaining three rooms are all of small dimensions and contain the three safes used for storing the radium used as solid salt, the radium in solution, and the filled radon applicators respectively.

The safe used for storing the radium in solution is lined with lead 15 cm. thick.

The solution is contained in 4 glass flasks (quartz vessels are being substituted for these) connected by glass tubing to the pumping and purifying plant in an adjacent room. Fig. 1. shows the interior of this safe.

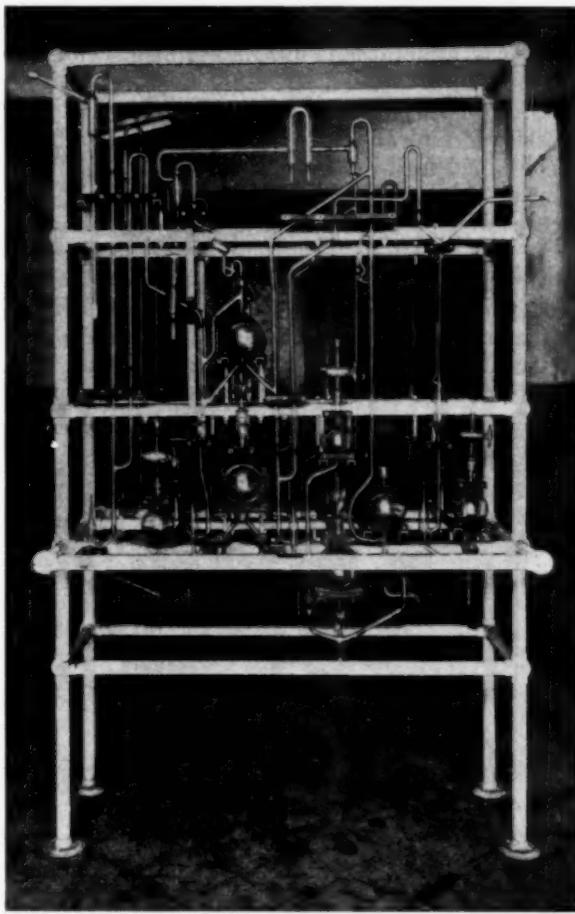


Fig. 2. Duplicate apparatus for extraction and purification of Radon (Ferroux type)

The apparatus installed for the extraction and purification of the radon was designed by Dr. RENÉ FERROUX of the Radium Institute of Paris, and is shown in Fig. 2.

It is built in duplicate on a single stand and does not require liquid air for its operation. Consequently, it is hoped that all interruptions of the service are eliminated, whether due to accidental damage to the apparatus or to the failure of supplies of liquid air. A reserve apparatus which, however, does require liquid air for its operation, is also included in the installation. The construction of this portion is based on the modification of HESS' apparatus (Phil. Mag. Ap. 1924) used at the Middlesex Hospital, London.

The room containing this plant is separately ventilated by means of a powerful electric fan, and can be darkened at will. It is also provided with a combined lead-lined work-table and fume cupboard. Here the sub-division of the glass capillary tubes containing radon is carried out, and the resulting «seeds» sealed into containers having any desired filtration.

The laboratory and workshop is equipped with a small precision lathe, tools for wood and metal working, glass blowing, etc., and a special electrometer due to Hollweck of Paris, used for measuring the gamma-ray activity of radon and radium applicators.

Special attention has been given to the problem of affording the personnel as complete protection as possible against the risks of injurious

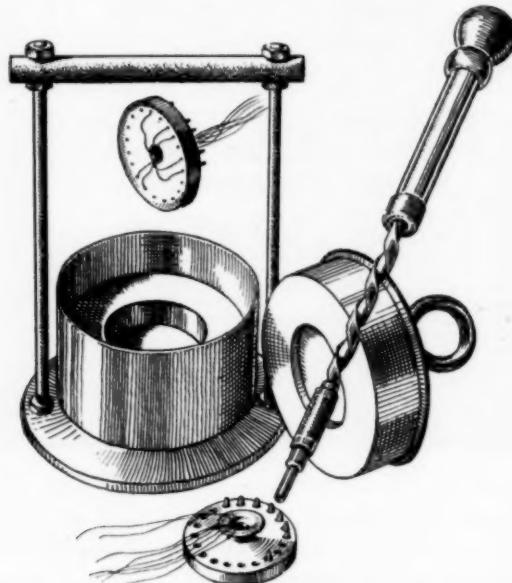


Fig. 3. Radon «seed holder», carrier and tool for sealing the seeds.

exposure to radiations. To this end, use is made of special appliances which facilitate the necessary manipulations of active containers. Further the number of such manipulations have been reduced to a minimum, and suitable lead protected tables, carriers, and safes provided.

Many of these appliances, such as special forceps, etc., are common to most institutions using radium, but several have been devised and first made at, or for, this hospital.

Illustrations of some of these are here shown. Thus, Fig. 3 shows a holder made of Monel metal with accommodation for 20 platinum-filtered radon seeds. The platinum »jackets» having been previously placed in position, the radon-filled glass capillaries are introduced and sealed into position by »burring over» the edge of the platinum by means of the automatic drill-fitting shown. The seeds are measured, stored, transported and sterilized in this holder. Its small size permits the use of a carrier (also shown) which gives a minimum protection of  $2\frac{1}{2}$  cm. of lead in all directions.

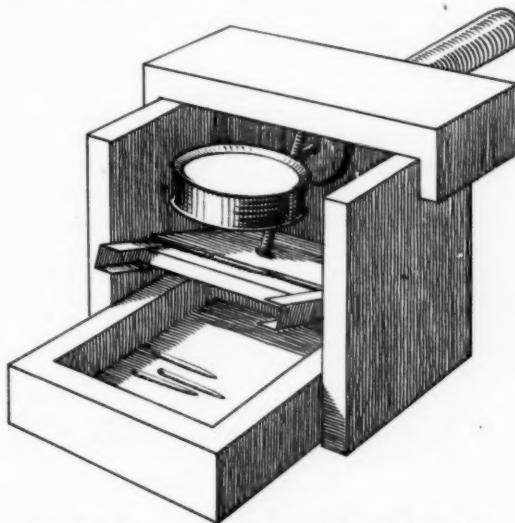


Fig. 4. Instrument used during 6 years for the rapid visual inspection of radium needles.

The device illustrated in Fig. 4 has proved of great value during the past 6 years for the visual examination of radium needles for identification or damage. The needle rolls down an inclined plane into the field of view of a magnifying lens. It is caused to rotate by pushing the handle of the lens, and after exposing every part of its surface to view, is finally projected over the edge of the inclined plane into the drawer

beneath. The thick lead walls on 5 sides afford ample protection to the operator.

Fig. 5. illustrates an instrument used for introducing radon «seeds» into cancerous tissue. The magazine attachment holds 8 seeds which

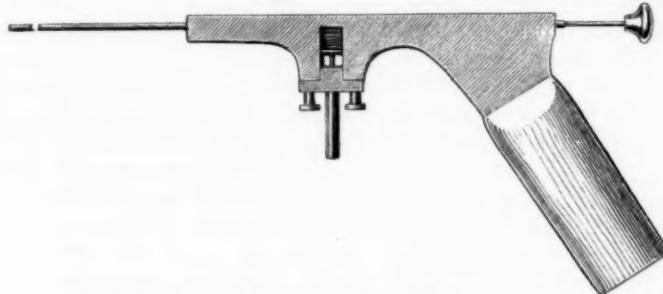


Fig. 5. Instrument for implantation of 8 Radon seeds in line.

can be expelled in a line with any desired spacing. It is commonly called «the gun».

#### Personnel

Under the direction of the physicist to the hospital, 4 whole-time assistants are required to carry on the work of the department.

Two of them are primarily concerned with the making of radon appliances and their standardization and measurement. The others deal with the issue and receipt of all radium appliances used in the various hospital departments and keep the records. All assistants undergo periodic (3 monthly) blood examinations.

#### General Organization

The general organization has already been described in the British Journal of Radiology, Ap. 1927, where full details of the rules enforced and forms employed, etc., are given.

It must suffice here to state that the Radium Department upon proper notice being given, delivers radium to all hospital departments, collects it when unused or after use, maintains all containers in repair, keeps them in safe custody when not in use and carries out routine tests and measurements.

A daily census is made of the number and location of all radium-salt containers, and complete records kept of the number of hours of use, damages incurred and repairs effected.

Similar records are kept of the production and employment of radon.

## SUMMARY

The Professor of Physics gives an account of the organization and equipment of the radium department of the Hospital. The total amount of radium element at the disposal of the Cancer Research Committee is at present 1100 mgr., but will shortly be increased to 1600 mgr. Of this, 500 mgr. are in solution and the remainder is distributed in several hundred platinum containers. The housing and equipment are described, together with the radium emanation plant designed by Dr. RENÉ FERROUX. Various details of the equipment are figured, and the general organization is summarised.

## ZUSAMMENFASSUNG

Der Verf., Professor of Physics an der Univ. London, berichtet über die Organisation und Ausstattung der radiologischen Abteilung des Krankenhauses. Die dem Cancer Research Committee zur Verfügung stehende Gesamttradiummenge beträgt gegenwärtig 1,100 mg, wird aber bald auf 1,600 mg erhöht werden. 500 mg davon sind in Lösung, die übrige Menge ist auf mehrere hundert Platinbehälter, verteilt. Verf. beschreibt die Räumlichkeiten und Ausstattung sowie den von Dr. RENÉ FERROUX entworfene Radium Emanations-Extraktionsapparat. Von verschiedenen Details der Einrichtung sind Abbildungen gegeben, und die allgemeine Organisation ist kurtz zusammenfassend beschrieben.

## RÉSUMÉ

Le professeur de physique rend compte de l'organisation et de l'équipement du service de radiumthérapie de l'hôpital. La quantité totale de radium dont dispose actuellement le Cancer Research Committee est de 1,100 mgr. mais sera prochainement portée à 1,600 mgr. Sur cette quantité, 500 mgr. sont en solution et le reste est réparti en plusieurs centaines de récipients en platine. L'auteur donne une description des bâtiments et de l'installation ainsi que des appareils d'émanations établis par le Dr RENÉ FERROUX. Un certain nombre de détails de l'installation sont reproduits et on donne une description sommaire de l'organisation.



## BIOLOGICAL EFFECTS OF RADIUM IRRADIATION

by

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When radiation first came into use as a therapeutic agent nothing was known of the way in which it acted or indeed might be supposed to act on the tissue irradiated, and the early history of Radiotherapy was based entirely on empiricism. The result of this was that nearly every patient was material for experiment, and though much valuable knowledge was attained, it was attained by trial and error and not infrequently, therefore, by disaster.

In recent years, however, research has been carried out on all sides and a scientific basis for radiological treatment, especially of cancer, is gradually being formed.

The first and most natural observations were those in which histological sections were made of the tumour at various times after irradiation in order to follow the course of its disappearance.

This was carried out by LACASSAGNE and MONOD (1) in Paris and by DONALDSON and the writer in this country. The results of the first fifty cases of the latter authors have been published (2) and to date about three hundred cases have been investigated.

The most important changes induced are: — cessation of mitosis which is immediate: the return of mitosis in large numbers and abnormal form in 3 to 4 days: disappearance of mitosis for the second time in 8 or 9 days: presence of cell débris which is removed by phagocytes: the replacement of the new growth by fibrous tissue: mummification which is of rare occurrence and found in certain cases where the destroyed new growth is not absorbed.

The observation of these changes was a comparatively easy matter, but the mechanism by which they were brought about was not so evident.

The question asked is: were the changes produced due to a direct action on the cell, or was the destruction brought about by some indirect method?

It was with the object of investigating this question that the late Dr. STRANGEWAYS and the various members of the Strangeways Research Laboratory at Cambridge began research on the effect of irradiation on tissue cultures, as by this means it was thought that it would be possible to study the effect on the cell isolated from the animal body, and therefore independent of blood and nerve supply and of possible formed antibodies.

The experiments show that a state of affairs could be brought about in tissue cultures similar to that brought about *in vivo* (3). With small doses of the gamma rays of radium (100 mg. of radium element filtered by 0.5 mm. of Platinum at a distance of 1.4 cm.) there was found to be a fall in the number of cells embarking on cell division, and the fall was followed by a return of mitosis shortly after the removal of the radium (Fig. I).

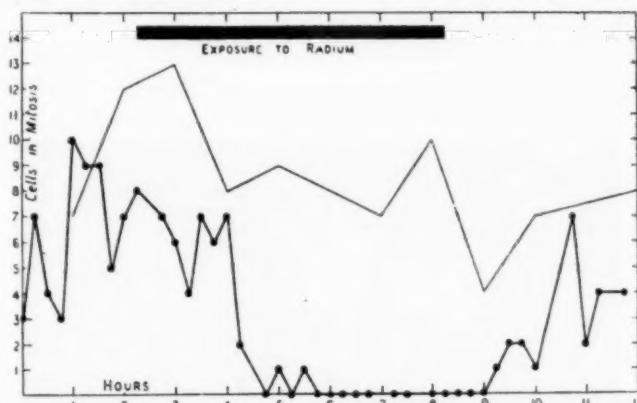


Fig. I. Graph showing the cessation and the return of mitosis in a tissue culture of chick choroid irradiated with 100 mg. of radium element filtered with 0.5 mm. of platinum at a distance of 1.4 cm. The thin line superposed shows the number of cells in mitosis in an unirradiated culture of the same age.

If the dose was somewhat larger, abnormal cell division began to make its appearance. Amongst other forms were unequal division of chromosomes and multipolar division. Both of these phenomena necessarily implied that the daughter cells thus formed would be deficient in chromatic content, and would therefore be likely to have altered characters. When however, an attempt was made by SPEAR to produce an immediate lethal effect, that is to say to give so much gamma irradiation to a

culture that no cells again went into mitosis, it was found that very large doses had to be given, and that they were of a size that would not be tolerated by the human subject. A similar result had been obtained by STRANGEWAYS and HOPWOOD (4) using X-rays. They found that 17,000 "e" units, i. e. approximately 100 erythema doses, did not immediately destroy more than a small number of cells.

These observations led to the hypothesis that the moderate doses of the order usually given to the patient produced a delayed lethal dose, that is to say that mitosis is not altogether inhibited, but is so deranged that the subsequent line of cells produced by division eventually dies out in one or more generations owing to the loss of certain of their essential characters. This hypothesis is still being investigated and has much to commend it, as the changes seen *in vitro* so closely resemble those actually found *in vivo*.

A naked eye demonstration of the effect of irradiation on mitosis is afforded by applying Radium emanation to a row of mustard or cress seeds, when it is seen that the hedge shows a gap where the radium emanation tube was placed and that the seedlings on either side grow less well both as regards roots and plumules.

The illustration (Fig. II) shows a drill of cress seeds, in the middle of which a glass tube containing 70 mcs. of radon was placed at the

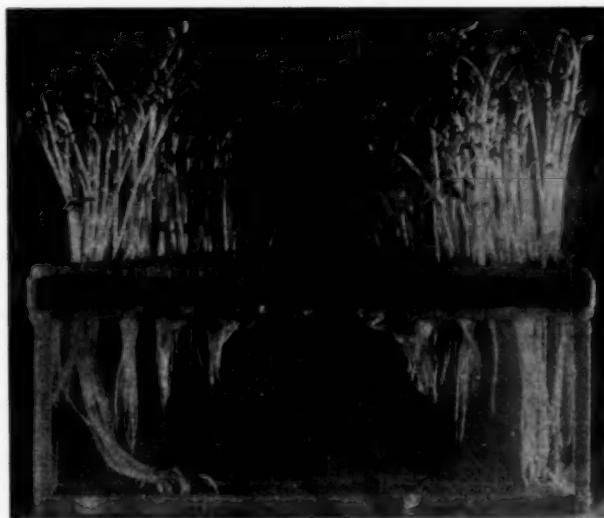


Fig. II. Drill of cress seed sown on gauze showing inhibition of growth of the roots and plumules produced by placing a glass tube containing radium emanation in the middle.

time when the seeds were sown. Both beta and gamma rays were therefore being employed.

The seeds were sown on gauze moistened by capillary attraction. When the seeds germinated, the roots passed through the meshes of the gauze into the water beneath. The curves formed by the tops of the plumules and the tips of the roots are clearly to be made out. It is also to be seen that the ends of the roots nearest to the source of irradiation have become bulbous.

The next step attempted was to try to find out whether it was more advantageous to give the same amount of radiated energy over a short time or a long time, that is, is it better to employ a large intensity for a short time or a small intensity for a long time.

As an indicator of biological effect, the diminution of the number of cells in mitosis in tissue cultures was selected (5). Batches of sixteen tissue cultures were taken and divided into two lots of 8 cultures each. One lot was kept as control and the other was irradiated with the required dose. Then both lots were fixed and stained, and the number of cells in mitosis in each culture was counted, those in the irradiated specimens being expressed as a percentage of those in the control specimens. Various determinations were then made with different intensities of irradiation for different times and the results were plotted as a graph.

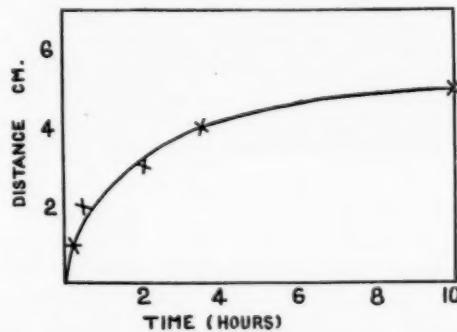


Fig. III. Curve showing the inhibiting effect on mitosis of chick fibroblasts produced by exposure to 100 mg of radium element filtered with 0.5 mm of platinum for various times at various distances.

From the results obtained it appears:

- 1) That there is a threshold of intensity below which no effect is obtained, however long the radium is left *in situ*.
- 2) That there is a threshold of time for each intensity which must be passed before the effect is obtained.

The first finding implies that under the conditions of the experiment a larger amount of radiated energy is required if the exposure is long than if it is short, that is to say, it is better to give a great intensity for a short time than a weak intensity for a long time.

Now this finding is in accordance with the recognised conditions for the production of skin erythema with X-rays, in which a greater amount of radiated energy is required if the exposure be long than if it be short. It is, however, not in accordance with the general clinical experience regarding the disappearance of neoplasms when treated with radium, for experience has shown that relatively long exposure to small quantities of radium are more advantageous than the high-intensity short exposures formerly given.

The reason for this discrepancy is not clear, but it does suggest in the case of the tissue culture and the skin that the result may be a direct action on the cell, and that in the case of new growths there may be an indirect factor playing an important part.

The work of several investigators points to this possibility. First Dr. HONOR FELL (6) working at the Strangeways Laboratory has irradiated chicks *in ovo* with X-rays. She finds that with a certain dose there is no immediate destruction of the chick at the 20—25th hour of incubation, that is before the vascular area is formed. If, however, the same dose is given to a 6 day embryo, i. e. after the blood vessels have formed, then there is thrombosis of the vessels following on destruction of the delicate blood vessel endothelium. This involves stoppage of the blood circulation and death of the animal, that is to say a lethal effect has been brought about by indirect action.

In another direction the work of LUMSDEN (7) at the Lister Institute suggests the formation of antibodies. He inoculates rats with Jensen's rat sarcoma into the pads of two feet. The tumour on one foot is treated with the serum of an animal immunized against Jensen's rat sarcoma. The tumour on the treated side disappears as might not unreasonably be expected, but this is followed by the regression of the non-treated tumour on the other foot. LUMSDEN attributes this regression to an active immunity produced by material absorbed from the attenuated or dying cells of the treated tumour.

Regarding selectivity, it is now known that certain tissues are more easily destroyed by irradiation than others and that this depends upon the activity of growth of the tissue. BERGONIÉ and TRIBONDEAU have formulated a law, the gist of which is that the more actively growing is the tissue, i. e. the more mitosis it contains at any one time, the more easily is it affected by irradiation. Thus tissues in human beings and animals, such as the skin and the testis, which are always in an active state of cell division, the former to replace cells lost by wear and the latter in

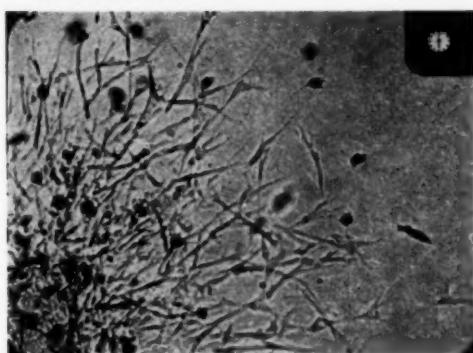


Fig. IV.

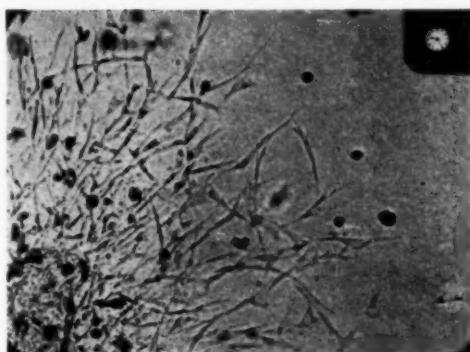


Fig. IV a.

*Culture of Chick Fibroblasts.*

Fig. IV. Before irradiation.

Fig. IV a.  $3\frac{1}{2}$  hours after irradiation with  $\beta$  and  $\gamma$  rays from radon (approx. 100 mcs. at 5 mm).

Note: (a) The cells have not moved their position.

(b) The shape of the fibroblasts is unaltered and they do not appear damaged.

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producing spermatozoa — are easily destroyed by irradiation, but the more fixed tissues, such as muscle, bone, connective tissue and brain, are hardly affected at all.

Now malignant new growths being actively growing tissue come under the same category as skin and testis and are easily destroyed by irradiation, whereas the surrounding tissues, if they be connective tissue or muscle, are relatively not affected. Further than this, clinical experience bears out theoretical findings, and it is found that such a tumour as a



Fig. V.

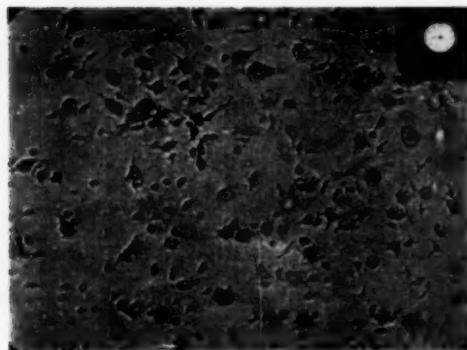


Fig. V a.

*Culture of Jensen's Rat Sarcoma.*

Fig. V. Before Irradiation

Fig. V a. 3 hours after irradiation with  $\beta$  and  $\gamma$  rays from radon (approx. 100 mcs. at 5 mm).*Note:* (a) The cells become shrunken and irregularly spherical.

(b) On the right hand side near the top is a cell arrested whilst undergoing mitosis.

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rapidly growing small round celled sarcoma will vanish in a short time whereas a more chronic form of tumour, for example a highly keratinized epithelium of the leg, will be more slow in disappearing. This time factor may well account for the relatively good results obtained in cases of sarcoma and for the less satisfactory results in cases of epithelioma when single doses of X-rays are employed, the exposure to X-rays being necessarily of short duration.

When one comes to investigate selectivity *in vitro*, the clinical find-



Fig. VI.

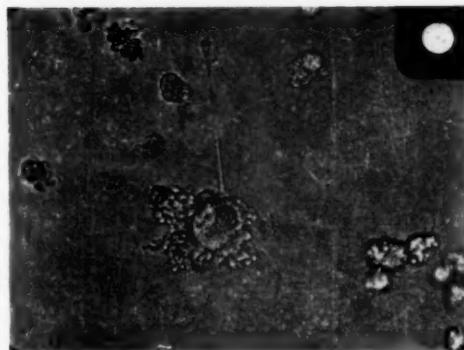


Fig. VI a.

*Culture of Jensen's Rat Sarcoma (high power).*

Fig. VI. Before irradiation.

Fig. VI a. 3 hours after irradiation with  $\beta$  and  $\gamma$  rays from radon (approx. 100 mcs. 5 mm).

Note: (a) The shrinking down of the cells into irregular spherical masses.

(b) The bubbles of cytoplasm over the surface.

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ings are fully born out. Pairs of illustrations cut out from a cinematograph film (8) show the condition of tissue cultures immediately before and three hours after the commencement of irradiation with a high intensity of beta and gamma rays from radium emanation. The first tissue photographed is the periosteum of the chick embryo. Before irradiation (Fig. IV) the culture showed plentiful mitosis and actively moving wandering cells. Twenty minutes after irradiation all mitosis had stopped, the movement of all the cells had ceased (Fig. IV a), and the

wandering cells became irregularly spherical in shape. After three hours the wandering cells had begun to disintegrate and the majority of fibroblasts, though immobilized, were apparently unaltered in appearance. The next pair of illustrations (Fig. V and V a) shows a culture of Jensen's rat sarcoma before and after irradiation. After irradiation all movement ceased in twenty minutes, and the cells became spherical and began to break down. The same effect is seen in the third pair of illustrations of Jensen's rat sarcoma taken under a high power. (Figs. VI. and VI a.). The effect of irradiation is seen much more markedly in the actual moving picture where cessation of movement takes place with great suddenness. From these pictures, then, it can be seen that the effect on the connective tissue cells, even with large doses of beta and gamma rays, is comparatively little, whereas the wandering cells, which include the leucocytes, and the sarcoma cells are affected to a marked degree and to about an equal extent.

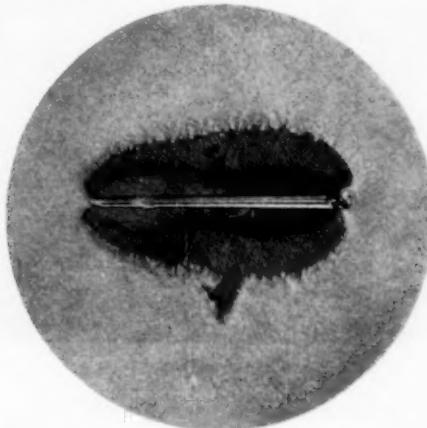


Fig. VII. Agar plate inoculated with *Streptococcus pyogenes* and *B. Coli* showing the differential inhibition of the growth of these organisms produced by a glass tube containing radium emanation.

Selectivity of action can also be shown in the case of bacteria. Fig. VII shows a photograph of a culture made by heavily inoculating an agar plate with a mixture of Streptococci and *B. Coli*. Placed on the surface of the agar plate thus inoculated was an unfiltered radon seed containing 7 mcs. The plate was then incubated for 24 hours. It is seen that immediately around the radon seed is a clear area showing no bacteria; outside this is an area containing Streptococci only and, still further out, is seen the edge of the growth of *B. Coli*. Thus the Streptococci are able to grow twice as near to the source of irradiation as the *B. Coli*,

that is to say, they are able to withstand approximately four times the intensity of beta irradiation.

There is one more subject to which reference should be made, and that is the Question of Stimulation. For many years there has been an idea prevalent that irradiation, especially if given in too small doses, causes stimulation. The chief reason for this appears to be that certain cases after treatment have developed a local recurrence or metastases with undue rapidity. More recently TODD (9), working at Bristol with Lead Selenide combined with X-rays, is of the opinion that the combination of these two forms of treatment is extremely dangerous, as the dose of X-rays given after the lead leads to the rapid growth of the tumour. In addition it has been suggested that the return of mitosis in a tumour three or four days after irradiation, to which allusion was made in the earlier part of the paper, is in fact an example of stimulation.

In the laboratory, attempts have been made at various times to show a stimulating effect, but so far no satisfactory evidence of direct stimulation has been forthcoming.

There is, however, one experiment which at first sight appears to give evidence of stimulation. During an investigation of the return of mitosis in tissue cultures (10) it was found that a certain dose of gamma rays, namely the energy irradiated in  $2\frac{1}{2}$  minutes by 100 mg. of Radium Element filtered with 0.5 mm. of platinum at a distance of 0.5 cm., caused a diminution of the number of cells in mitosis to 40 % in 1 hour 20 minutes, and that the number of dividing cells returned to normal in two hours. The number of cells in mitosis however continued to rise till the end of the fourth hour when 160 % of the normal was reached. After this the number fell to normal, where it remained till the termination of the experiment. The mitosis counts were made on batches

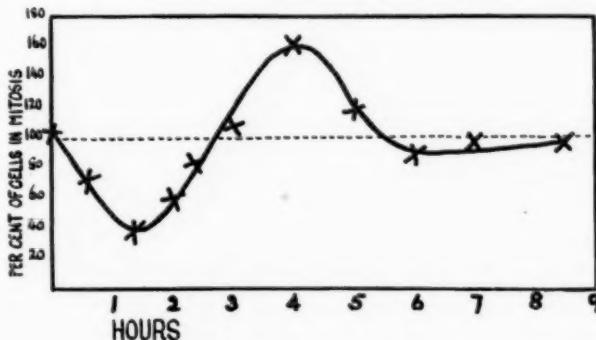


Fig. VIII. Curve showing the fall and subsequent rise in the number of cells in mitosis after radium irradiation.

of tissue cultures as already described and were adequately controlled. The results are plotted as a curve (Fig. VIII). The reason for the increased number of dividing cells may be due to one of two causes, viz. either the number of dividing cells is increased, or the number actually remains the same, but the time occupied by the process of cell division is longer, so that at any one time there are a larger number of dividing cells to be found. In neither case can it be said that there is any true stimulation, for if the rise is due to a larger number of cells entering mitosis, then it is found only to be compensatory to the fall which had previously occurred.

### SUMMARY

The paper describes first the earlier observations on the histology of tumours irradiated with the gamma rays of Radium. The difficulty in interpreting the results led STRANGEWAYS and his co-workers to the study of the effect of radiation on tissue cultures. The cessation and return of cells undergoing division is described and the hypothesis of delayed lethal dose considered. An experiment is described affording a naked-eye demonstration of the effect of beta rays on a row of cress seeds. The «time-intensity» ratio is then considered and from the results of experiments on tissue cultures it appears that there is a threshold of intensity and a threshold of time, each of which must be passed before a biological effect of radiation can be obtained. Comparison of the time factors employed in these experiments and by radiologists leads to the subject of «indirect action» which is briefly discussed. Selectivity of action of gamma rays on cancer cells is illustrated by cuttings from cinematograph films of tissue cultures of normal and malignant (Jensen's rat sarcoma) cells, and a photograph is given demonstrating the selective action of beta rays on *B. Coli* in an agar culture of Streptococci and *B. Coli*. Reference is made to «stimulation» and an experiment described on tissue cultures showing an increase in cell division which might erroneously be considered the result of stimulation.

### ZUSAMMENFASSUNG

Die Arbeit beginnt mit einer Beschreibung der früheren Beobachtungen über die Histologie von Tumoren, die mit Gamma-Radiumstrahlen bestrahlt worden waren. Die Schwierigkeit der Deutung der Resultate führte STRANGEWAYS und seine Mitarbeiter zum Studium des Effekts der Bestrahlung auf Gewebekulturen. Verf. beschreibt das Verschwinden und Wiederkehren von Zellteilung und erörtert die Hypothese einer hinausgeschobenen letalen Dosis, bei welcher Zelltod in einer der nächsten Zellgenerationen eintritt. Es folgt ein Bericht über ein Experiment, das es erlaubt, die Wirkung von Beta-Strahlen auf eine Reihe von Kressesamen mit freiem Auge zu beobachten. Sodann wird das Verhältnis »Zeit-Intensität» in Betracht gezogen; nach den Resultaten der Experimente an Gewebekulturen scheint es, dass ein Schwellenwert der Intensität und ein Schwellenwert der Zeit existiert, die beide überschritten werden müssen, bevor eine biologische Wirkung der Bestrahlung erhalten werden kann. Der Vergleich des bei diesen Experimenten und des von den Radiologen verwendeten Zeitfaktors führt zu dem Thema »indirekte Aktion», das kurz erörtert wird. Durch Ausschnitte aus Kinematogra-

phenfilms von Gewebekulturen normaler und maligner (Jensens Rattensarkom-) Zellen wird die Selektivität der Wirkung von Gamma-Strahlen auf Karzinomzellen illustriert. Ferner wird eine Photographie wiedergegeben, welche die selektive Wirkung der Beta-Strahlen auf *B. coli* in einer Agarkultur von Streptokokken und *B. coli* demonstriert. Bezugnehmend auf die »Stimulation«, beschreibt Verf. einen Versuch an Gewebekulturen, der eine Steigerung des Zellenwachstums zeigt, die irrtümlich als Resultat von Stimulation betrachtet werden könnte.

### RÉSUMÉ

Le présent travail communique d'abord les observations antérieures concernant l'histologie des néoplasmes irradiés aux rayons gamma de radium. La difficulté que présentait l'interprétation des résultats conduisit STRANGEWAYS et ses collaborateurs à étudier les effets des radiations sur des cultures histologiques. On donne une description de l'arrêt et de la régression des cellules en voie de division, ainsi que des considérations sur l'hypothèse de la dose mortelle retardée. L'auteur décrit une démonstration visible à l'œil nu de l'action des rayons beta sur une série de graines de cresson. Il considère ensuite le rapport »durée-intensité«; il résulte des expériences faites sur cultures histologiques qu'il existe ici un seuil de l'intensité et un seuil de la durée qui doivent être chacun préalablement franchis avant qu'on n'observe une action biologique des radiations. Une comparaison entre le facteur durée mis en œuvre dans ces expériences et le facteur durée utilisé par les radiologistes conduit l'auteur à la question de l'action indirecte qui est brièvement discutée. La sélectivité de l'action des radiations gamma sur les cellules cancéreuses est illustrée par des coupes provenant d'un film cinématographique de cultures histologiques de cellules normales et malignes (sarcome du rat de Jensen); une photographie indique également la sélectivité des radiations beta sur le colibacille dans une culture sur agar de streptocoque et de colibacille. L'auteur rappelle la théorie de la »stimulation« et décrit une expérience effectuée sur des cultures histologiques en montrant une augmentation de la division cellulaire qui a pu être interprétée à tort comme un résultat de la stimulation.

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## THE THERAPEUTIC USES OF RADIUM APPLIED EXTERNALLY

by

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For a number of years after radium began to be used in medical work in 1903 it was applied almost entirely by external methods. That is of course apart from its insertion into the cavities of the body-mouth, vagina, rectum and oesophagus, etc. The introduction of radium tubes and needles into the tissues probably started with the discovery of DOMINICI that the really valuable rays in the treatment of malignant disease were those which passed through at least a millimetre of lead. Glass tubes containing radium or emanation had, it is true, been introduced into the tissues, but in spasmodic and haphazard ways and, for many years, practically all the treatment was done by external applications. Lack of radium and lack of sufficient knowledge of the principles governing its action, retarded the development of external methods and resulted in the introduction and development of methods of burying radium in the tissues for deeply-placed disease. Surface disease was still treated by surface applications.

Later still the introduction of the use of large quantities of radium again made possible the use of external application for deep disease. The further discovery that the use of small quantities of radium for a long time was beneficial in certain forms of new-growth resulted in the utilization again of comparatively small amounts of radium for external treatment and made its use much more widely practicable. This method does not supplant the use of large quantities at a distance, for these can be made much more effective so that they cause much less inflammatory reaction. Therefore the use of large quantities at a distance, which probably started with myself in 1911,<sup>1</sup> and was much furthered by the

<sup>1</sup> I used over 600 mg. on a bladder case.

loan of 5 grammes to the Middlesex Hospital by the Medical Research Council in 1920 for 6 months, has been the subject of special development of technique and apparatus. There seems little doubt that the future lies in this direction, but the problems of protection and continuous utilization of so much radium are very big ones.

### Treatment of Superficial Diseases

By superficial diseases we mean those which do not extend to more than 1 cm. below the surface. They may originate in the skin or the subcutaneous tissues.

The rays utilized are different with different workers. There is a natural tendency to use the least penetrating rays, because they exist in much greater quantity, but in some cases it is certain that they are not as valuable as the more penetrating radiations. In other cases there is more room for difference of opinion, and it is quite possible that the  $\beta$  rays have their uses and even the  $\alpha$  rays. These latter are difficult to obtain in practice, owing to their feeble penetration, a layer of paper or protective tissue being sufficient completely to cut them off.

#### *Differences in Action of $\beta$ and $\gamma$ Radiations.*

The  $\beta$  radiations are seldom used pure, but when a thin filter is used they preponderate to such an extent that their action must predominate.

The latent period of the effect of the  $\beta$  rays is much shorter than that of the  $\gamma$  rays, being only one or two days. There appears to be more swelling of the endothelium of blood-vessels with the  $\beta$  than with the  $\gamma$  rays. On a malignant growth the  $\gamma$  rays have a much more selective action than the  $\beta$ , at any rate the  $\beta$  rays of lesser penetration. Nevertheless the action of the  $\gamma$  rays may quite possibly be due largely to secondary  $\beta$  rays formed in the tissues. I have seen the less penetrating rays give an area of loss of pigment from the skin surrounded by an area of increased pigmentation and this I have not seen from the  $\gamma$  rays.

#### *Methods of Application.*

The radium may be made up in square or circular plaques or discs. The emanation may be put into a flat glass vessel of similar shape. Owing to the action of radium in causing many materials to oxidize readily, the method of keeping the radium in place and protecting it from external injury presents great difficulty unless heavy filtration is used. Various forms of varnish used to be employed, but most of them tended to crack and allow the radium to escape. Dental composition was used for some

time at the Radium Institute, but this also cracked in time. Of late years we have used Monel nickel and copper alloy metal of a thickness of 0.03 mm.

Provided that the less penetrating  $\beta$  rays are not required, it is possible to fashion a plaque out of a number of needles placed touching one another on a piece of strapping. Such an arrangement has the enormous advantage that it can be curved to any extent in one direction and can therefore be moulded to a curved surface. If the softer rays are required, the needles may be made of Monel metal or of rustless steel. If only the harder rays are to be used they are made of platinum or gold.

For some surface lesions a single radium tube is ideal, especially when the lesion is oval or rectangular. It can also be used with advantage on a circular lesion by placing it for half the time in one direction and for the other half at right angles to this: a circular zone of action results.

#### *Filters.*

If the caustic action of the radium is required in addition to its selective action on the deeper parts, no filter other than the varnish or Monel metal of the apparatus, with the addition of a thin layer of protective tissue, need be used, but, for most things, a metallic filter of more or less absorptive power will be used.

*Separating material* (which also filters off the secondary rays formed in the primary filter).

In treating superficial disease this will not usually require to be of any great thickness.

For cleanliness sake a little protective material such as gutta-percha tissue or oil-silk will be used over a varnish applicator. When a metallic applicator is used, a thin layer of rubber or one or two of lint will be required to cut out the secondary radiations. With rather deeper lesions thicker material will be necessary than with the more superficial ones.

### **Superficial Diseases Treated by Radium**

#### **Malignant Neoplasms**

##### *Epithelioma.*

Small superficial epitheliomata are often mistaken for rodent ulcers, unless a section is examined. Sometimes they are recognized by not responding as readily to radium treatment.

A small quantity of radium applied for a long time, appears to have a very definite advantage in such cases, even when they have either failed to respond to large doses for a short time or when they have recurred after

such treatment. There seems also no doubt as to the value of heavy filtration in such cases: 0.5 mm. of platinum or corresponding amounts of other metals being the minimum, as was shown by DOMINICI more than twenty years ago. A heavier filtration than this is thought by many of us to give even better results. Good results have been obtained in many of these cases by burying radium needles deep to the lesion. When the growth is very extensive or has involved bony structures, radium on wax as described below will be required.

Two methods of treating these cases are in use:

- 1) the caustic, and
- 2) the selective.

1) When the caustic method is employed the healthy skin around the growth is protected by lead 1 mm. thick leaving a rim of healthy tissue 5 mm. wide all round the growth. Very lightly filtered radium (0.03 mm. of Monel metal) is then used, generally in the form of a plaque, and about six times the skin erythema dose is given. In this way the superficial parts of the growth receive a dose which causes their destruction, while the deeper extensions, if any, receive only the selective dose. The lesion is found to heal readily in a few weeks, leaving a soft scar. In the author's opinion there is a great tendency to recurrence after this method.

#### *Dosage.*

The dose will vary with the size of the tumour. If this is less than 1 cm. diameter, a plaque 2 cm. square will just cover the area leaded off. Such a plaque covered with 0.03 mm. of Monel metal would be used for 5—6 hours on end or for a longer time, if the dose is spread over more than one day. With larger tumours and correspondingly larger applicators containing 5 mg. per square centimetre, the time will be a little shorter, owing to the radiations from the other parts of the plaque slightly increasing the dose.

2) The selective method does not go far enough to cause obvious destruction of tissue. It may be applied in one series of applications extending usually over one, two or three weeks. Such applications are as nearly continuous as possible. They may be made by burying radium needles in the subcutaneous tissues or by applying radium on the surface. In the case of small growths as small a quantity as half a milligram may be used.

The method used by the author in rodent ulcers (q. v.) is sometimes sufficient with small epitheliomata.

The use of large quantities for a short time is definitely less effective and cases which have been treated in this way and have recurred, may sometimes be cured by the slow method.

**Dosage.**

Radium needles buried 1 cm. apart in the subcutaneous tissues, with a strength of 0.66 milligrams per centimetre active length, require to be left in for 5—8 days. If, for instance, 7 needles, 3 cm. active length, were used, they would be left in for 5— $5\frac{1}{2}$  days.

If the needles are closer together, as they will be in small lesions, the time may be lessened, but, if only two or three needles of 1 mg. are used, the total amount is so small that 7 or 8 days will be necessary.

**Rodent Ulcers.**

1) The caustic method may be applied with greater success than with epitheliomata, as the tendency to recurrence is less. The scar is a little more obvious than with the selective method.

2) For twenty years the author has found the following method extremely effective for small rodent ulcers: it is a selective method.

A tube of 53 mg. of Ra., active length 15 mm., with a platinum filter of 0.5 mm. and a rubber filter of 1 mm., is used. If the lesion is circular and small enough, the tube is placed in one direction for 35 minutes and then at right angles to this for another 35 minutes. If the lesion is oval the tube is used in one direction only for 65—70 minutes.

This treatment is repeated after 6 weeks and again in another 6 weeks, until two prophylactic doses have been given after all visible sign of the disease has gone.

If for any reason it were necessary to cure the growth with one application only, the tube would be left on about 1 hour in each direction, but the reaction which resulted would be severe.

3) For larger rodent ulcers or for those which do not respond to the above methods, it will be necessary to use other technique, either burying radium needles in the subcutaneous tissue deep to them or else using a surface application on wax as described below. By the latter method the author has been enabled to get rid of rodent ulcers which have become epitheliomatous, although they have been treated for many years with radium by the caustic method. Cases also have been treated by burying radium needles under an obstinate recurrence with great success: whether this was due entirely to using a small quantity for a long time is not certain, but it is probably the factor of chief importance. The dosage is the same as for epithelioma.

**Benign Neoplasms****Angeioma**

In most forms of naevi, radium is the treatment *»par excellence»*. It leaves far less scar than any other method and can be used not only

for those naevi which involve the skin, but also for subcutaneous angioma.

When the skin is involved there is always likely to be some damage caused by the naevus, which the radium will of course not remove, but it is always much less than one would expect.

With port-wine stains it is more difficult to get a good result than with other forms, as one tends to get a certain amount of blotching.

Spider naevi are usually best treated by other methods the electric needle or sparking, as these are quicker and, if properly done, leave no scar.

Whatever the type of naevus, it is best treated when the child is quite young. The younger the child, the more effective the treatment: in adults the improvement is only partial as a rule.

Another rule is to leave a very long interval between the treatments, as improvement goes on for 6 months or even a year after an application. If the dose is too large it may be followed by telangiectases, one, two or three years after the treatment.

The dose of radium in a child under 1 year is about 55 % of that given to an adult and so on until a full dose is given at about the age of 16 or 17.

I always use a filter of 0.5 mm. of platinum (or 1 mm. of lead), as too small a filtration may lead to loss of pigment in the treated area with increased surrounding pigment and thus a notable scar.

A number of needles or tubes placed side by side, touching, on a piece of strapping forms a very good flexible applicator. With 13 such needles each containing 5 mg. of radium and having an active length of 2 cm. and with a filter of 0.5 mm. platinum and a secondary ray filter of 1 layer of lint, the dose, in an adult, is  $2\frac{1}{2}$  hours and, in a baby of 6 months, 1 hour 22 minutes. With notably fewer needles the length of time increases slightly.

I also use a 50 mg. tube, active length 15 mm., with 0.5 platinum filter and 1 mm. of pure rubber as a secondary filter. It is moved about to different areas if the naevus is large enough. The dose with such a tube in an infant under 1 year is 36—37 minutes on one area, 35—36 minutes if two areas are treated and so on.

Some swelling of the naevus usually occurs during the first twenty-four hours after the application. This soon subsides and then the naevus gradually but very slowly gets paler so that little change must be looked for before 3—4 weeks.

#### *Papilloma.*

The value of radium in this condition is not fully realized. Naturally if there are many scattered warts the treatment may not be appli-

cable, but if most of them can be treated and got rid of, the rest will disappear without treatment.

Occasionally one meets a case where no response is shown to the radium treatment at all, but the vast majority respond well to an erythema dose.

The most valuable use of radium in this connection is in the treatment of corns on the feet, both hard and soft. As the skin on the heel and on the ball of the foot is very thick, the dose is larger than on the skin of the face, increasing by as much as 50—100 % above that used for parts where the skin is thinner. Also, the corn itself sometimes separates the radium so far from active parts of the skin, that a similar increase in dosage may have to be employed. With this proviso the dose is similar to that used in the selective treatment of rodent ulcers, except that one application only, without repetition, is necessary for each corn or wart.

#### *Keloid.*

This condition responds well to radium treatment, but no better than to X-rays as a rule; so that in general the latter will be preferred except in young children. Whichever treatment is used, it should be done in the earliest stage possible and there must be a long wait for the result. The scar remains widened to the extent to which it has been increased by the keloid, but it becomes quite soft, smooth, flat and painless.

### **Inflammatory Diseases of the Skin**

#### *Eczema.*

Usually this disease is too extensive for safe treatment with radium, but when localized it can be treated and responds well to small doses. Acute cases require only one-eighth of an erythema dose repeated on two or three successive days, but chronic cases require rather bigger doses. Very lightly filtered rays have mostly been used for this condition.

#### *Psoriasis.*

The lesion disappears, but recurs after a varying interval. Continued repetition leads to permanent skin damage, with resulting ulceration if a local infection occurs, which is very difficult to heal.

#### *Lichen Planus.*

Responds well in some cases. The radium must not be too lightly filtered.

*Lupus Erythematosus.*

This responds well to lightly filtered radiation.

*Lupus Vulgaris.*

Very variable results have been obtained and, as a general rule, radium will not prove the best treatment for this condition. Sometimes, however, very successful results have been obtained when other methods failed. If mere destruction is aimed at, diathermy or other caustic will be better than radium. When the selective action is required, it will be necessary to use fairly heavy filtration, Pt. 0.5 mm.

*Leucoplakia.*

Screened radiation (Pt. 0.5 mm.) will get rid of this condition, but will not prevent its recurrence. Two-thirds of a skin erythema dose may be used for a single application, or smaller doses with repetition of the treatment.

*Hypertrichosis.*

The treatment of this condition with radium is fraught with danger and is often not advisable. Its use needs the greatest care and experience and the dosage will not be discussed here.

*Cicatrices.*

With recent scars much softening may be produced: when older, the effect of radium is not so good, but still of use.

*Dupuytren's Contraction.*

Much may be done by radium treatment of this condition, particularly in its early stages. A full dose of  $\gamma$ -rays is given to the affected region.

**Preparation of the Surface Treated**

All crusts must be removed. If the lesion is very septic a preliminary zinc ionization may be very helpful.

**Treatment of deep Disease by External Applications***Separating Material.*

Felt, lint, wood, paper and other materials have been used, but most people now employ «Columbia wax» which is a mixture of hard paraffin, beeswax and sawdust. The sawdust sinks into the bottom of the molten waxes and this lower surface is applied to the skin. The compound

can be easily moulded if raised to a temperature slightly above that of the body.

The radium is, of course, applied on the surface farthest from the skin.

The thickness of the wax is 1.5 cm. and one or more layers of this may be used. When a distance of 6—8 cm. is required, an air-space is left between two layers of wax, as otherwise the apparatus would become impossibly heavy: cork is used to keep the two layers at the correct distance.

Cork blocks fitted on to a celluloid splint have been used for a similar purpose, but the wax is probably better, as it is a better scattering medium for the rays.

#### *Distance and Dosage.*

The greater the distance of the radium from the surface of the body, the greater will be the dose received by the deeper parts relative to that received by the skin: the actual dose received by each will be less. The law of inverse squares, however, does not apply because the source of radiation is not a point.

The employment of large distances necessitates the use of much radium and a special technique has been developed for quantities of radium of 1 grammme and upwards. A special apparatus has to be used for holding it in position and for shielding the operator, and the parts of the patient not being treated, from the rays. As the rays are very penetrating, large quantities of lead must be used and they are very heavy. In Paris, as much as 4 grammes have been used in such an apparatus. The apparatus is sometimes arranged for treating two patients at the same time either side by side or one above the other. Its exact value in radiotherapy is as yet not determined. It is often referred to as a «radium bomb».

In England 1.5 cm. is the distance usually employed, occasionally 3 cm. This short distance is necessary on account of the small quantity of radium usually available. In Paris and Brussels where larger quantities are used, a distance of 6—8 cm. is much more usual.

One advantage of the use of smaller quantities of radium has been the necessity of increasing the time of the total application. If this extends over more than 3 weeks, the latent period is reduced to one or two days, and if the application lasts over more than 4 weeks, the latent period is almost entirely suppressed. The great value of this is that one knows that the reaction will not get appreciably more severe, after one removes the radium: on the other hand, it needs courage to carry the reaction to the full extent necessary when the patient suffers much discomfort. With short distance applications, e. g. 1.5 cm., it is necessary

to go far enough to get a little vesication of the skin. With greater distances this does not prove to be necessary. The wax applicator must be retained in close contact with the skin.

The approximate amounts used are as follows:

For both sides of the neck — 80 mg.

For one side of the neck — 50 mg.

For supraclavicular and pectoral regions — 120 mg.

The applicator is worn for 16 hours a day in the case of the neck, and 18—22 hours a day in the case of the breast. The application for 16 hours etc. need not be continuous, but can be split up as the patient prefers, as long as 16 hours treatment is given in each 24 hours.

In some cases, especially in breast carcinoma, it will be advisable to diminish the dose of radium and use X-rays as well, and one finds that approximately 50 % of each are required, or say 75 % radium with 25 % X-rays.

After the first fortnight, the patient should be seen every day in order to determine when to stop the application, and this is not done until vesication commences, unless there is very marked erythema before the end of the three weeks, in which case allowance must be made for its getting more intense.

#### *Preparation of the Applicator.*

The wax is first of all placed in water at 115° F. (46° C.) and the water is kept at this temperature. It takes about 20 minutes for the wax to get soft enough to mould easily. When it is soft, it is carefully moulded to the part to be treated and then set by cooling in cold water. The construction of the radium containers usually permits them to be heated in a spirit flame; they can then be stuck on to the wax, but not buried deeply in it. The whole is covered with adhesive strapping so that, if it cracks, it does not fall asunder. These operations do not take long to describe, but they take a very long time to carry out.

#### *Effects during the Application.*

If the patient has much pain, this usually gets worse for a day or two and then gradually disappears. Narcotics may be necessary for a few days.

There is usually some increase in the urine in the early stages of the application and the patient should be encouraged to drink freely.

The pulse-rate increases after a few days and then gradually comes back to normal.

If the application is made to the neck, there is, after a few days, perversion of taste and some loss of taste, often complete, during, and for a few days after, the treatment.

There is usually a considerable amount of asthenia in the later stages of the treatment, particularly in a breast case. When the neck and face are treated, there is much dryness of the mouth, with stickyropy mucus, and, in the later stages of the treatment, much soreness of the mouth and throat with the formation of a white film over the mucous membrane.

#### *Treatment of the Skin.*

If there is only slight vesication and it is possible to keep the parts dry, the best application is powdered zinc stearate or a mixture of this with bismuth carbonate. Usually, however, an oily application is necessary. Following Mr. BOND and Mr. CADE I have used a solution of radiostol in liquid paraffin and found it very successful. Otherwise one may use Linimentum Calaminae with 0.2 % of phenol. If there is any septic infection the application of a 1 : 2,000 flavine dressing covered with oil-silk for a few days will soon clear it up.

Should there be much pain, the best application is an ointment containing 5 % of cycloform in lanoline.

#### **Conditions Treated by these Methods**

The glands in a growth of the upper air passages are best treated in this way either after surgical removal or without this. The treatment seems insufficient to cure the primary growth itself, so this must be dealt with separately by radium needling or diathermy. It seems better than radium needles or seeds in the neck, as the rays are distributed so much more homogeneously. The use of a radium bomb in such cases as also deep X-rays will also attack the primary growth.

This method can also be used for breast carcinoma, particularly for recurrent growths and, for this treatment, may be combined with penetrating X-rays. We have had such satisfactory results in primary breast cases with radium needling that we prefer this method for such cases. When the supraclavicular glands are involved, however, the radium collar, possibly combined with radium needling, seems the better method.

The radium applicator may also be used for the groins in treating carcinoma of the vulva or of the penis. It has also been used in brain tumours after a preliminary decompression.

As mentioned above, certain superficial growths will also have to be treated in this way.

#### **Dangers and After-effects**

The primary vesication always heals in a short time, if no previous application has been made. It is not quite so quick or so certain in the case of second or third applications.

It has been stated by REGAUD of Paris that a second treatment should never be given on account of the growth's becoming radio-resistant. I hold that most growths become radio-resistant in their later stages, whether previously treated with rays or not. In some cases in my experience so much good can be done by a second or third application, that it should not be withheld on purely theoretical considerations.

In a few cases which have had severe irradiation, a late necrosis of bone or cartilage has taken place which is extremely resistant to any treatment. It is always an infection of damaged tissue and is much more likely to occur after more than one irradiation. In France extensive resections of bone or cartilage have been undertaken to prevent this trouble, but as some bone or cartilage is always left this operation does not seem sound. The removal of all septic teeth is of the utmost importance before any irradiation is attempted, in preventing this trouble.

It must be understood that these methods are at present in the course of elaboration and development, and nothing that is final can yet be written about them. The dogmatic statements in this article are merely intended as a guide to those not already practising this treatment as to where to start their investigations.

## SUMMARY

The author sketches the history of the external uses of radium since 1903, and records that he was probably the first to use a large quantity at a distance in 1911. The methods of application are described, together with their use in superficial diseases such as epithelioma, rodent ulcer, and inflammatory diseases of the skin. The treatment of deep disease by external application is then described, with a consideration of the separating material (usually Columbia wax), distance and dosage, effects during the application, and treatment of the skin.

## ZUSAMMENFASSUNG

Verf. skizziert die geschichtliche Entwicklung der äusserlichen Verwendung des Radiums seit dem Jahre 1903 und erwähnt, dass er — im Jahre 1911 — wahrscheinlich der erste war, der eine grosse Menge Radium auf Distanz verwendete. Verf. beschreibt die Applikationsmethoden und ihre Anwendung bei oberflächlichlokalisierter Krankheiten, wie bei Epitheliomen, Ulcus rodens und entzündlichen Hautkrankheiten. Sodann ist die Behandlung von tiefssitzenden Leiden durch Aussenapplikation beschrieben, unter Berücksichtigung des separierenden Materials (gewöhnlich Columbiawachs), Distanz und Dosierung, Wirkung während der Applikation und Behandlung der Haut.

## RÉSUMÉ

L'auteur esquisse un historique des usages externes du radium depuis 1903 et rappelle qu'il fut probablement le premier à faire usage de fortes doses et d'application à distance, en 1911. Il décrit les méthodes d'application en même temps que leurs usages dans les affections superficielles, telles que l'épithélioma, l'ulcus rodens et les affections inflammatoires de la peau. Il donne ensuite une description du traitement des affections profondes par applications externes, ainsi que du matériel spécial utilisé (vernis de Colombie), des distances, des dosages, de l'action au cours de l'application et du traitement de la peau.



## RADIUM TREATMENT OF CARCINOMA OF THE RECTUM

by

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### Introduction

Radical surgical treatment of Cancer of the rectum in the last 15 years or so has reached a high standard of efficiency, but it remains an operation with a considerable mortality (not less than 10 % for all types of radical operation), and it inflicts on the sufferers the stigma of colostomy.

The chances of permanent cure, given an adequate radical operation, are in direct proportion to the degree of mobility of the growth, and the chances of secondary metastasis following operation increase with the degree of fixation until a stage of fixation is reached which is regarded as inoperable, because there is then little or no hope of radical cure. Between the early operable and the late inoperable there are the borderline cases which in the past, in expert hands, have been submitted to operation or not according to the age, general condition and associated circumstances of the case.

It is perhaps in the border-line cases that radium will prove to be of most service.

### Radium Therapy

The vista which is opened up by the study of a new line of treatment is extremely fascinating. The physicists have prepared the ground for the surgeon over long years of study, ably supported by scientific investigators who have studied the action of radium on animal tissues. Yet to-day most of our radium therapy in combination with surgery of access is still in the experimental stage, though moving with ever increasing rapidity, as the volume of clinical experience grows, in the direction of standardization.

When a radical operation for malignant disease is undertaken, the surgeon has behind him the history of the surgical attack for that disease, and the great volume of past experience of generations of surgeons.

To-day the surgeon working with radium, with no long past to guide him, is developing his attack, trying out methods, testing dosage and checking results in a limited field, seeking the optimum method, and the optimum dose, and knowing that on the one hand an incomplete attack spells failure, and on the other that too aggressive methods may overwhelm both diseased and healthy tissues.

It is thus evident that all radiological work must be approached in a spirit of research, and that the results of every case must be studied in all its aspects for future guidance.

It is just as essential for the surgeon, who desires to practise radium therapy, to study the subject at the clinics of those who have most experience in the subject, as for the young surgeon to go through a course of operative surgery before undertaking surgical operations.

### Rectal Radium Therapy

Although radium has been employed in the treatment of cancer of the rectum in this country for 30 years or so, it is only within the last five years that we have attempted to treat the disease by a combination of surgery and radiation.

Our present knowledge of the effects of radiation does not allow accurate deduction to be made as to the changes which may be expected to follow a given type or degree of radiation.

Tissue response depends upon several varying factors. At the present time it is not possible to control our radiological treatment from the histology of the tumour under treatment. We know that the more specialised the malignant cell, the more radio-resistant it is, and the more the type conforms to embryonic tissue the more radio-sensitive it is.

Adeno-carcinoma of the rectum has in the past been generally regarded as very radio-resistant. My experience of the last five years leads me to believe that this is by no means the case, and that this impression has arisen from the difficulty of access as compared with the cervix uteri, the tongue, the breast, etc.

With the help of surgery a fair proportion of low rectal carcinomas can be exposed from behind and mobilised in such a way as to give access to all parts of the tumour, so that a uniform barrage can be secured.

Further, high growths which extend above the peritoneal reflexion can be dealt with successfully, though with greater risk, by approach through the peritoneal cavity.

Experience shows, in favourable cases, when the optimum dosage has been secured, that in both situations carcinomas which are regarded as unsuitable for excision can be destroyed, and the patient restored to health, although in the majority a permanent colostomy is a necessary penalty.

Further, when a rectal carcinoma has advanced to such a stage of fixation as to prevent adequate access by open operation, much may be done by intra-rectal attack with needles or seeds to reduce the size of the growth, to relieve haemorrhage, mucous secretion, pain and tenesmus, which often continue to make the life of a patient suffering from advanced rectal cancer extremely miserable, even though a colostomy relieves the rectum of its normal function.

Experience has shown that by holding the carcinoma in check in this way, not only are symptoms relieved, but the general condition of the patient is often improved beyond all expectation.

### Indications for Radium

The following advantages can be secured by the use of radium appropriately applied in adequate dosage:

#### A. In cases too advanced for radical surgery

- 1) The growth in some instances can be reduced in size and rendered sufficiently mobile to permit of excision.
- 2) A certain percentage of cases will respond so well that the *growth can be destroyed* and a cure result.
- 3) In the most advanced cases pain can be relieved, haemorrhage checked, and excessive secretion reduced.
- 4) Local rectal recurrences following excision, and secondary glands in the groin following excision of growths involving the anal canal can be completely destroyed.
- 5) Radium may be employed as a measure secondary to deep X-ray therapy<sup>1</sup> in cases too advanced for radical treatment with radium by open operation to be attempted. Preliminary treatment by deep X-ray therapy may produce improvement, so that radical radium treatment becomes possible.

<sup>1</sup> This article is not concerned with the employment of deep X-ray therapy, but the author has employed deep X-ray therapy in conjunction with radium both before and after radium therapy. Clinical evidence points to deep X-ray therapy being more useful before, than after, radium, but experience is too limited at present to express any definite views on combined treatment.

**E. In cases considered suitable for radical operation, but in which a radical operation is contra-indicated on other grounds or is refused by the patient, radium offers high hopes of a cure**

**C. In cases favourable for radical operation**

The author's experience with radium in this class is limited, but such excellent results have been secured in a few cases as to warrant the opinion that in the near future we may be able to place radium on an equal footing with radical surgery, or even higher, and in some instances to avoid the stigma of colostomy which is essential to sound radical surgery.

**Early Technique**

The earliest attempts to treat cancer of the rectum with radium not infrequently resulted in burns followed by sepsis due to inadequate filtration, and though in sporadic instances cures were recorded, in the majority more harm than good was accomplished. At that time the method employed consisted in passing a flexible probe into the rectum, so that a tube containing 50 mg. or more of radium was implanted into the lumen of the growth; in other instances a rectal tube, with a tube of radium fixed within it, was passed down the colostomy opening through the growth to the anus. Gauze was then sewn round the tube below the point where the radium was fixed, and the tube then drawn up so that the radium was engaged in the growth and was prevented by the gauze from going up beyond the growth. The great objection to this method of employing radium in bulk is that a heavy dose is delivered to the area of growth in contact with radium and a weak dose to the periphery, and that the time factor is too short.

So long ago as February 1910, a medical man suffering from carcinoma of the rectum was treated by my colleague, Dr FINZI, with a 50 mg. tube of radium in the lumen of the rectum. I had the opportunity of examining the case before treatment and at a later date when all evidence of growth had disappeared. This patient remained free from recurrence up to the time of his death some 10 years later when over 70 years of age.

Although since that time I have had cases treated in similar fashion and seen relief from symptoms, I have seen no other cure. It is evident when we consider the wide extent of most inoperable growths of the rectum that it is not possible by this method to secure even radiation of all parts of the growth in the majority of cases.

This method has now been replaced by the use of filtered radium needles or radon seeds employed in such a way as to deliver as far as

possible a uniform barrage of gamma rays to all parts of the growth, and also to the area of lymphatic spread and for such length of time as to secure if possible that all the malignant cells are activated by the gamma rays to the point of saturation.

### Dosage

The main problem of cancer radiation lies in dosage, and the optimum dose in any individual case is arrived at by experience. Herein lies the danger of placing radium in the hands of the inexperienced. As already stated the difficulty of access is a great handicap to uniform radiation of many rectal growths and thus compares unfavourably with the tongue and breast. The needles employed in the majority of cases treated from the perineum have been filtered with 0.5 mm. of platinum, but with a recent supply of radium the filtration has been increased to 0.6. Three, two, one, and half-milligramme needles have been used with a linear intensity of 1.6 centimetres per milligramme. The long 3 mg. needles are used for the lymphatic areas. The growth itself is radiated in a uniform manner, and needles of different length used according to the thickness of the growth as indicated in the diagrams. In some cases the needles are inserted at right angles to the surface, in others parallel or oblique to the surface, the method varying according to the general shape and thickness of the growth. An approximate standard of dosage is aimed at of one milligramme per cubic centimetre of growth and the growth is assumed to extend for a centimetre beyond its palpable margin.

The needles have been left in for varying periods, but the average has been ten days for the perineal and seven for the abdominal.

In abdominal radiation with needles one and half mg. needles have been used for the growth itself and sometimes larger ones for the lymphatic areas. Quite recently some shorter half-milligramme needles have been used within the abdomen which are only ten millimetres long and therefore not much longer than seeds.

When radon is employed, seeds of about two millicuries filtered with 0.5 mm. platinum or gold have been used and inserted at intervals of about half an inch. In most cases they are not removed.

Experience suggests that it is wise to err on the side of small doses within the peritoneum. At the present time, when needles are used, they are removed after five days.

### Methods of Attack

The following methods, with the exception of (7), have been adopted by the author for radiation of rectal carcinoma, separately or in combination.

- 1) Barrage by open operation from the perineum.
- 2) Intra-abdominal radiation.
- 3) Intra-rectal radiation
 

	needles,
	seeds,
	tubes.
- 4) Radiation through the vagina.
- 5) Radiation through the perineal skin.
- 6) Surface radiation (on Columbia paste).
- 7) Distant «bomb» therapy will be employed when sufficient radium is available.

#### **1. Needle Barrage by open Operation i. e. Radiation after Exposure of the Growth from the Perineum (after the method of NEUMANN)**

This method is most suitable for growths involving mainly the infra-peritoneal portion of the rectum and especially those which involve the posterior portion of the bowel. It can also be employed for annular growths, for growths involving the anal canal and the lower portion of the supra-peritoneal (i. e. pelvic) portion of the rectum.<sup>1</sup> The method is inadvisable for very advanced growths which have passed the boundaries of the rectum and become firmly fixed in all directions, because adequate exposure is difficult or impossible, and is likely to result in laceration of the growth and rupture of the rectum, and to be followed by serious sepsis.

If secondary suppuration has followed invasion of the ischio-rectal fossa with growth, radium is contra-indicated.

This method may be combined (in the female) with radiation through the posterior vaginal wall when the anterior wall of the rectum is involved as well as the posterior, and in the male it may be combined with the use of radon seeds inserted through the skin to attack the anterior portion of the growth, either at the same sitting or on a separate occasion.

A preliminary colostomy is usually regarded as essential to keep the rectum at rest and to minimise the dangers of sepsis during treatment.

Under exceptionally favourable conditions when an early growth is attacked, it may be possible to avoid colostomy or to close the colostomy at a later date, but in inoperable and advanced cases a permanent colostomy becomes essential, because in the process of cure fibrosis replaces the growth and stricture follows.

During the past year, as a tentative measure in a few cases without marked stenosis, perineal barrage has been undertaken without opening the abdomen or performing a colostomy. This is a procedure which can

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<sup>1</sup> The best approach for the pelvic portion of the rectum is via the abdomen.

be adopted with most likelihood of success for the early operable case, when excision has been refused or is contra-indicated, and when it can reasonably be assumed that there is no metastasis in the liver. It is advisable (when needles are employed) to keep the bowels locked up until the needles are removed. Prior to the barrage a very thorough clearance of the colon is carried out for three days. In more advanced cases it should only be attempted with growths involving the lower part of the rectum and mainly confined to the posterior wall. It is unlikely to succeed with an annular growth, or with a growth which has caused marked narrowing of the lumen.

There are certain obvious disadvantages in not opening the abdomen and performing colostomy.

1) There may be metastasis in the liver which makes the radium treatment futile.

2) Passage of faeces through the rectum may cause sepsis and inhibit successful radiation.

3) Healing following radiation may result in fibrous stricture and so render a colostomy obligatory.

#### Technique of Perineal Operation

Before the perineal stage of the operation can be undertaken, a median or left mid-rectus laparotomy is carried out from ten to fourteen days in advance, when the liver is investigated for secondary deposits. The extent and fixation of the growth from above is then ascertained and glands are felt for in the meso-rectum, meso-sigmoid and iliac regions. Whether glands are present or not, it is advisable to insert radium into the meso-rectum along the line of the inferior mesenteric vessels and, if the growth extends above the peritoneal reflection, into the meso-sigmoid also. If glands are discovered, radium should be inserted beneath the peritoneum alongside them.

If needles are employed they should be threaded with silk. A total of from 3 to 6 mg. is used for the retro-rectal space according to the presence of palpable glands or not, and roughly 0.5 mg. radium per palpable gland in the mesentery or iliac regions; this is left in for 7 days. An anaesthetic is often required to remove them.

When radon seeds are available they are used in preference to needles and can be left permanently *in situ*, which is a distinct advantage, and the colostomy can be opened earlier if required.

A hypogastric colostomy (first stage) through the laparotomy wound in the mid-line is then carried out and the strings attached to the needles are brought out through the lower end of the wound and the ends, to which beads are attached, are left under the skin which is sutured over

them. The colostomy is left unopened if possible, until the radium is removed at the end of the week. If preferred a second incision in the iliac fossa may be used for the colostomy and the radium strings brought out through the median wound.

#### The Perineal Stage

After the colostomy has been established and the radium removed from the abdomen, the lower colostomy opening should be utilized to wash out the rectum thoroughly for a few days before the second stage of the operation.

The patient lies on his face with the legs hanging over the table and, after temporary suture of the anus, an incision is made from an inch above the sacro-coccygeal junction to an inch behind the anus, and extended laterally to either side of the anus for about two inches. The coccyx is removed, the fascial median raphé incised, and the levatores ani separated and retracted. The ampulla of the rectum is thus exposed. The rectum is then carefully freed from the sacrum above, the pelvic floor on either side, and the interval between it and the prostate in front, if the growth involves the anterior wall, is defined. This is carried out so as to expose the growth as freely as possible.

#### Glandular Attack

The next step is to radiate the lines of lymphatic spread along the inferior and middle haemorrhoidals, and also the superior haemorrhoidals if this has not been done from above.

One 3 mg. needle (4.8 cm. active length) with silk attached is passed outwards into each ischio-rectal fossa and above each levator ani muscle (vide diagram fig. 2), and two 2 mg. needles are passed upwards in the retro-rectal space one centimetre on either side of the middle line.

#### Barrage of Growth

The growth is barraged in a uniform manner and with proper regard to its thickness. If the growth is thin, it is usually advisable to remove the temporary stitch from the anus and to pass the needles with the left finger in the rectum. Two, one, and half-milligramme needles are used for the growth, with 0.5 or 0.6 platinum filtration the latter preferred. An attempt is made as far as possible to deliver 1 mg. of radium in parallel lines to each cm. of growth, to avoid penetration of the mucosa, and to radiate for a centimetre beyond the free margin of the growth. In practise, especially in advanced cases, owing to the irregularity of the growth and inaccessibility of some parts, it is

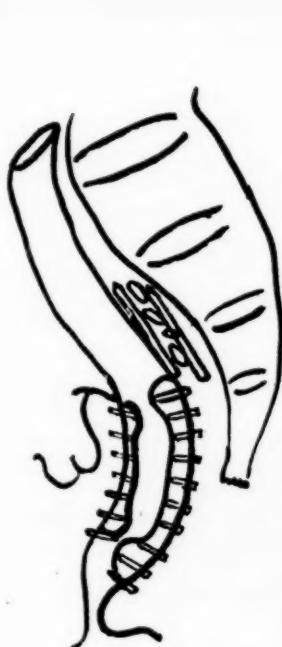


Fig. 1.

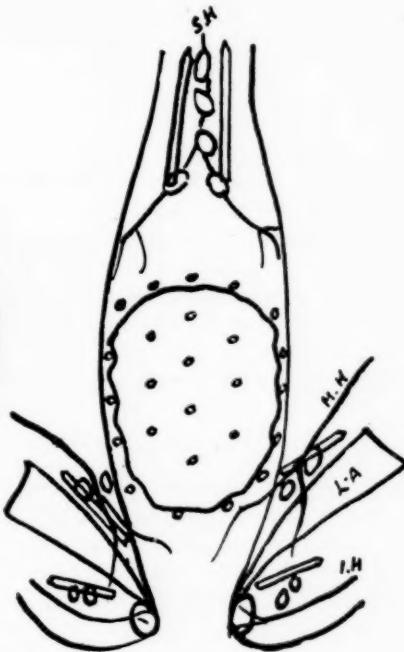


Fig. 2.

frequently difficult or impossible to carry out this scheme accurately or thoroughly. The general idea is indicated in diagrams (fig. 1 & 2).

In the female when the anterior wall of the rectum is involved, needles are passed into the growth in a similar manner through the posterior vaginal wall.

About thirty to sixty milligrammes are usually employed according to the size of the growth, and the needles are left in for 10 days. The silk threads attached to the needles are then tied together and buried in the wound. Gauze soaked in paraffin and flavine is packed over them, and a catheter is embedded in the gauze. The wound is closed temporarily with sutures and is subsequently kept moist with flavine solution which is instilled in small quantities at regular intervals. If this precaution is not adopted, it is difficult to avoid a septic wound which heals very slowly. In most cases the radium has been left in for ten days. If reaction is unusually severe, the needles are sometimes removed earlier. Under the most favourable conditions these wounds are slow to heal. A dense white fibrinous film forms on the radiated area, which separates

slowly. In some instances when ulceration has thinned the growth, radiation is followed by perforation of the rectum which further delays healing. Ultra violet light has proved very helpful in accelerating healing.

Moderate cystitis is a common complication and is best avoided by tying in a catheter for the first four or five days.

#### Biopsy

Whenever considered desirable, a portion of growth is removed for section. Usually this has been done at the time of the colostomy operation by means of a special punch. In other instances a portion has been removed at the same time as the needles are removed. By the latter method there is less likelihood of stimulating metastasis. When early growths have been dealt with, it has been considered inadvisable to disturb the growth for the purpose of biopsy.

### 2. Intra-abdominal Radiation

Growth which are situated above the peritoneal reflection may be attacked through the peritoneum either with radon seeds or radium needles. As already stated, seeds (filtered with 0.5 platinum) present the advantage that they need not be removed, but there are not sufficient data available to show whether, owing to the diminishing intensity, they are as effective as needles.

The patient is placed in the high Trendelenburg position and the small intestines are packed off from the pelvis with towels. The glandular areas are dealt with as described for the perineal operation. The growth is treated in a similar manner to that adopted in the perineum, but very short needles are employed and great care is taken to avoid penetration of the mucosa. Access may be very difficult.

If there is any doubt as regards penetration at the time of radiation, it is wise to pack off the area of growth and remove the packing with the needles.

When the growth is partly above, and partly below, the peritoneum the lower portion of the growth can be attacked at a subsequent operation by inserting seeds via the lumen of the rectum through a proctoscope.

The pelvic colon is brought out through the upper end of the wound in readiness for colostomy. When needles are used the strings are collected and brought out through a rubber tube at the lower end of the wound and removed after seven days, if possible before the colostomy is opened.

In some cases the results have been remarkable and in one of the author's cases the colostomy was never opened. In this case the tumour

was fixed to the bladder and there was considerable stenosis. The patient is at work and remains well and free from evidence of growth 18 months after treatment.

In other instances inflammation of the pelvic peritoneum has occurred with ileus. In view of the fact that the peritoneum is not greatly disturbed by the radiation in the majority of cases, it seems probable that a leak or excessive necrosis has been the cause when peritonitis occurs (*vide infra*).

### 3. Intra-rectal Radiation

This method is reserved mainly a) for very advanced cases as a palliative measure for relief of symptoms when radon seeds are usually employed.

b) For some cases where patients are considered too infirm for surgical measures.

c) For small early growths which are easily accessible and which may then be cured without any surgery. In such cases, should radium fail, successful excision can still be carried out.

Radium is introduced either by sight through a proctoscope or by touch with a finger in the rectum.

### 4. Radiation through the Vagina

Radiation through the vagina may be supplementary to perineal barrage (*vide supra*) or employed as the main attack for anterior growths. The needles are inserted in a uniform manner guided by a finger in the rectum and a gauze pack soaked in flavine left in the vagina.

Some excellent results have been secured by this method. In one instance an inoperable annular growth which had caused a recto-vaginal fistula was treated by vaginal radiation only with the intention of subsequently employing perineal barrage. Following vaginal treatment the fistula closed and the growth became mobile and operable. Perineal excision was carried out and the patient is alive and well 3 years after operation.

### 5. Radiation through the Skin of the Perineum

Squamous-celled carcinoma involving the anal skin can be treated like carcinoma of the tongue with a ring of needles or seeds through the skin. If the inguinal glands are involved they can either be treated by radical excision, implantation, or surface radiation on Columbia paste. If there are no palpable glands it is advisable to employ prophylactic surface radiation to the inguinal glands on Columbia paste. If the anal growth extends upwards in the anal canal it can be barraged in a similar manner via the skin. This method is preferable to direct puncture of

the growth which may result in some haemorrhage, or even sepsis, and is not without risk as regards stimulation of metastasis.

The method is also useful in advanced and extensive adeno-carcinoma of the lower end of the rectum when radical radiation is not considered possible. These patients often suffer great distress from tenesmus and the discharge of blood and mucus.

Seeds can be inserted through the skin round the growth, directed by a finger in the rectum, in such cases taking due precaution to avoid puncture of the urethra or bladder.

This procedure causes little disturbance to the patient and in some cases has resulted in alleviation of symptoms, diminution of the growth, and proved very beneficial. There is no need to remove the seeds.

#### 6. Surface Radiation on Columbia Paste

This may be used for a) epithelioma involving the anal skin, b) perineal recurrence, c) the inguinal region either as a primary treatment or to supplement implantation.

The author has employed it successfully in all three directions.

#### 7. Distant »Bomb« Therapy

Distant »bomb« therapy has been employed in America and on the Continent and some good results have been claimed.

Shortage of radium has up to the present prevented the use of the »bomb« at St. Bartholomew's, a shortage which it is hoped will be made good in the near future.

#### Irradiation in Association with Excision of the Rectum

The conversion of a border-line or inoperable case into an operable case by means of radiation has already been referred to, and the use of radium applied to lines of lymphatic spread upwards (i. e. along the inferior mesenteric vessels) through the peritoneum during the preliminary operation of colostomy has already been advocated. The practical value of the former procedure has been demonstrated; as regards the latter procedure, it can at least be said that it is rational, even in the absence of tangible metastasis, provided that no serious risk attaches to the procedure. When palpable, hard enlarged glands can be demonstrated, radiation provides the only hopeful method of attack. Experience shows, however, as the result of frequent histological investigation after excisions and from an occasional biopsy, that often enlarged glands behind the rectum show no evidence of metastasis, but only chronic inflammation.

So far, in a limited number of cases, no untoward effects have followed this procedure. On the other hand abdominal radiation of a high rectal growth is not without danger and fatalities have occurred from a low grade pelvic peritonitis and fatal ileus. There is not as yet sufficient evidence available to say whether these ill results have been due to faulty technique and faecal leakage as a direct result of implantation, or to secondary sepsis following too intensive irradiation producing necrosis, but the latter explanation, from a study of two fatal cases, seems most likely. In most, though not all, of the cases treated through the abdomen there has been a mild pelvic reaction followed by some inflammatory discharge from the pelvic drain, and it seems probable that if the radiation is too intense some tissue necrosis may result and the fatal train of symptoms follow.

It is desirable, therefore, to err on the side of caution in dosage within the abdomen; to use small needles of not more than 1 mg. each, with a filtration of 0.6 platinum as a minimum, and to allow not less than one and a half centimetres interval between each needle, and further to exercise extreme caution in their introduction.

Sufficient experience has not yet been gained to compare the value of radon seeds and radium in this respect, but undoubtedly the technical risks are less when the former are used. There is less danger of perforation owing to the small size of the seeds; they need not be removed and consequently require no threads leading to the surface which may interfere with the fixation and stability of the needles and perhaps provide a path to sepsis from the surface. The method is on trial and should not be undertaken lightly by the inexperienced. Radiation *after excision* must undoubtedly be of value when a growth has been removed which has spread beyond the confines of the rectal wall. It sometimes happens that an excision is undertaken for a growth which is assessed as borderline, but which turns out to be more fixed than anticipated. Under these circumstances the excision cannot be classed as radical and such assistance as can be gained by radiation of the periphery of the involved area is most certainly indicated, though the value of the measure can only be assessed after a long period by statistical investigation.

#### Radium for Recurrence.

In the past a local recurrence of carcinoma following excision of the rectum has seldom been amenable to successful surgery. In some instances favourable response to deep X-rays has been noted, but these results have been of a temporary nature. I have been able to treat a few of these patients quite effectively with needles combined with external radiation on Columbia paste. No patient has been under observation long

enough to express an opinion as to cure, but results so far have been much more encouraging than could have been anticipated.

### Results

This paper is based on the experience gained with the treatment of 65 cases of cancer of the rectum with radium, during the past  $4\frac{1}{2}$  years.

It has been demonstrated a) that an early growth on the anterior wall of the rectum can be destroyed by needling through the vagina, and that the rectum at the site of growth can be restored to its normal appearance and calibre, and b) that a similar result can be secured by introduction of seeds directly into a small growth; c) that a large fixed inoperable growth can be destroyed by perineal radiation with a resultant fibrous stricture and remain well ( $3\frac{1}{2}$  years); d) that an inoperable high growth can be apparently cured by abdominal radiation, and further that a colostomy is not always essential; e) that a fixed inoperable growth can be rendered operable; f) that a perineal recurrence can be made to disappear; g) that the worst and most advanced cases can be made more comfortable by relief of symptoms.

It is true that the successful cases form a small percentage of the total, but the fact that radium can accomplish these results is a great encouragement to persevere. In nearly every case some benefit has followed, in most there has been marked improvement though many of these have relapsed.

### The relative Values of Surgery and Irradiation

I do not think that any of us who are in the habit of operating on cancer of the rectum have any doubt in our minds that we can cure cancer of the rectum in the early stages (except in the very young) by means of surgery, provided that the patient will submit to colostomy and can survive the radical operation. If early diagnosis was the rule instead of the exception, the surgical results of radical cure would stand comparison with those of cancer in any other region of the body. The reason for this confidence is that, save in exceptional circumstances — for example, in very young subjects — glandular and visceral metastasis occurs late in the disease.

Radical surgery for cancer of the rectum may be criticized on the score of mutilation in that a colostomy is essential and a reproach to surgery. Although I do not regard a well-managed colostomy as a great handicap in life — and I can produce many professional and business men, who follow their vocations with little hindrance, to support this view — I do feel that when we see what can be done with the tongue,

for example, we ought to explore the field of radium to the utmost in an endeavour to supplant radical surgery.

I have on many occasions expressed my views as to the ideal surgical treatment of rectal cancer, and I still hold that colostomy followed by the modern perineal excision is the best procedure for all mobile growths in the rectum proper, reserving the abdominal-perineal operation for growths at or above the recto-sigmoidal angle.

The time may come — it may even be within measurable reach — when we shall have such certain control of the action of radium that we shall be able to say, as it can at the present time, I believe, be said of many cancers of the tongue and cervix: »This case, though suitable for a radical surgical operation, can be cured with greater certainty, with less risk, and — greatest boon of all, if it comes — without any permanent disability, with radium».

Until we are in a position to measure the action of radium with some accuracy, to be able to say with confidence that a given dose of radium administered in a given way for a given time will produce a certain result, we are, I think, in duty bound to advise radical surgery, mutilating though it is, in preference to radium for the operable case. Where, however, as sometimes happens, the growth is operable, but the patient is considered unsuitable for radical surgery on other grounds, then I believe radium holds out great prospects of cure, and should always be employed when available.

It is quite possible that in the near future rectal irradiation may be so regulated as to offer as high a percentage of cures, *in early cases*, as by operation and with less risk, and in a certain number without the inconvenience of colostomy. For the inoperable case, provided that there is no secondary perirectal sepsis, invasion of the bladder, or metastasis in the liver, radium should certainly be recommended.

In recent years experience with radium in the treatment of carcinoma of the tongue has produced such remarkable results that those who practise radium therapy have for some time past ceased to excise the tongue. Carcinoma of the cervix uteri stands on the same footing, and, judging by the results which are now being obtained with radium in the treatment of cancer of the breast, it will not be long before those surgeons who have access to, and experience with, radium will cease to amputate the breast. I hope to see the time when the same can be said of excision of the rectum.

When passing in review the results of my work with radium during the past five years I do not doubt that, with increasing experience, I shall be able to cure year by year a higher percentage of inoperable cases, and I am satisfied that with judicious selection of cases I can assist those who have passed beyond the hope of cure by alleviating their symptoms and prolonging their lives.

## SUMMARY

The author considers the relation of radium treatment to operation for rectal carcinoma. He concludes that radium should be used chiefly for inoperable and border-line cases, and then only in conjunction with surgery. He gives an account of the indications for radium, the technique, dosage, and methods of attack. Neumann's method of irradiation with needles after exposure of the growth from the perineum is described in detail, with diagrams showing the distribution of needles. Other methods are considered more briefly, namely intra-abdominal, intra-rectal, through the vagina, through the skin of perineum, surface radiation on Columbia wax, and irradiation with a bomb at a distance. The author has in a few cases used irradiation as a preliminary to excision, but the method is still under trial. Some patients have also been treated for recurrences after operation. In all 65 patients have been treated in  $4\frac{1}{2}$  years, and the results have been, on the whole, encouraging. The author is satisfied that great alleviation can be obtained in advanced cases, though he does not at present prefer radium treatment when the growth can be removed by operation.

## ZUSAMMENFASSUNG

Verf. stellt einen Vergleich zwischen der radiologischen und operativen Behandlung des Rektumkarzinoms an. Er kommt zu dem Schluss, dass Radium hauptsächlich für inoperable und Grenzfälle angewendet werden sollte, und auch dann nur in Verbindung mit chirurgischer Behandlung. Er gibt einen Bericht über die Indikationen der Radiumverwendung, ihre Technik, Dosierung und Angriffsmethoden. Neumanns Bestrahlungsmethode mit Nadeln nach Freilegung der Geschwulst vom Perineum aus ist unter Beifügung von Diagrammen über die Verteilung der Nadeln im Detail beschrieben. Andere Methoden, nämlich die intraabdominale, intrarektale, durch die Vagina, durch die Perinealhaut, die Oberflächenbestrahlung unter Montierung auf Columbiawachs, die Bestrahlung mit einer Bombe per distance, sind kürzer erörtert. In einigen wenigen Fällen bediente sich der Verfasser der Bestrahlung als Vorbehandlung einer Inzision, diese Methode wird aber noch erprobt. Manche Patienten wurden auch wegen Rezidiven nach einer Operation bestrahlt. Im ganzen wurden in  $4\frac{1}{2}$  Jahren 65 Patienten bestrahlt, und die Resultate waren im grossen ganzen ermutigend. Verf. ist überzeugt, dass in vorgeschrittenen Fällen grosse Erleichterung zu erzielen ist, anderseits zieht er bis jetzt die Radiumbehandlung nicht vor, wenn die Geschwulst operativ entfernt werden kann.

## RÉSUMÉ

L'auteur expose le rapport existant entre la radiumthérapie et le traitement opératoire dans le cancer du rectum. Il conclut que l'on doit surtout recourir au radium dans les cas inopérables et dans les cancers de la marge (dans ces cas, comme complément du traitement chirurgical). Il donnent les indications du radium, le dosage, la technique et les méthodes d'attaque. Il décrit en détails le procédé de Neumann d'irradiation à l'aide d'aiguilles, après découverte de la

tumeur par le périnée et donne des diagrammes indiquant la répartition des aiguilles. Il expose brièvement d'autres méthodes, et notamment la méthode intra-abdominale, la méthode intra-rectale, la méthode transvaginale, transpérinéale, l'irradiation superficielle avec vernis de Colombie, et l'irradiation à distance à l'aide d'une bombe. L'auteur a recouru dans quelques cas à l'irradiation préalablement à l'excision, mais la méthode est encore en voie d'études. Quelques malades ont été également traités pour récidives consécutives à une opération. 65 malades en tout ont été traités en 4 ans et demi et les résultats sont, à tout prendre, encourageants. L'auteur constate avec satisfaction qu'une amélioration notable peut être obtenue dans les cas avancés bien qu'à l'heure actuelle, il ne donne pas la préférence au radium tant que la tumeur peut être extraite opératoirement.



## RADIUM TREATMENT OF MALIGNANT DISEASE OF THE UPPER AIR PASSAGES

by

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Since 1912 researches in Radium therapy have been carried out in our department and many different types of growth have been treated. For advice regarding the physical and biological aspects of radium we are indebted to Prof. Hopwood and Dr. CANTI, but the pioneer of this treatment at our hospital has been Dr. FINZI who has given us invaluable assistance in deciding the best method of treatment and the dosage for individual cases. Also we owe much to many continental colleagues especially to Prof. REGAUD (Paris) and Prof. BAYET (Brussels) for their kindly help and advice.

After fifteen years' experience we have gradually come to the conclusion that radium, often in combination with some form of surgery such as diathermy, has certainly given better results than surgery alone. There is evidence to show that it has lessened the tendency to early recurrence; moreover it has made it possible to benefit many cases that would previously have been considered inoperable, either because they were too advanced or were so highly malignant that good results could not be expected to follow excisions. As is now well known, the highly cellular growths such as round-celled sarcomas and Grade 1 carcinomas are, in many respects, favourable for ray treatments but not for operations. Whenever possible radium should be buried in the tissues and as a rule small doses should be used for long periods. With smaller doses and better technique our results have gradually improved.

**Malignant Growths involving the Nasal Fossae or Accessory Sinuses including Carcinoma, Endothelioma and Sarcoma**

Previous to 1912 malignant growths arising in these regions were always treated by surgical operations. Although in many of these types the growths were localized and showed no tendency to disseminate either to the glands or to distant organs, the results obtained by operations were unsatisfactory; and in a series of twenty-three cases treated by one of us only three survived for periods of more than five years. In the remainder, early recurrences occurred in the bones surrounding the cavities and were generally so extensive as to be considered inoperable. Another drawback to treatment by operation was the fact that many of the growths were found to have invaded the bones so deeply that it was impossible to excise them completely. Since 1912 all our cases have been given ray treatment.

**Methods Employed**

*Transpalatal.* By removal of the hard palate together with the teeth and alveolar process of the affected side of the jaw, the growth can be exposed from below. Access can thus be obtained to a growth originating in the antrum, in the nasal fossae, or even higher in the ethmoidal region. It can then be freely excised or destroyed by diathermy. After all obviously diseased tissue has been removed, the cavity is treated with radium, preferably at once. Two methods have been used, namely, a single large tube containing 50 to 100 mg. of radium with a filter of 2 mm. of platinum wrapped in as much gauze as the cavity will accommodate and retained for 24 to 48 hours; or a series of radium needles containing 1 to 2 mg. of radium with 0.5 mm. filters uniformly applied to the surface of a mould of the cavity in Stent's Dental Wax, and retained for several days. With either method it is advisable to irradiate the pterygoid region from the post-nasal space as described later, or by needles inserted through the mucous membrane posterior to the last upper molar tooth. And it may be necessary to supplement the treatment by insertion of a few outlying needles through the skin around the affected cavity, or by X-rays. In considering the dose it is important to give as much radiation as is considered necessary to destroy the disease, irrespective of the damage that may be done to normal tissues. In all cases some necrosis of the bony cavity will result, and in rare instances the eye will suffer.

The transpalatal method has many advantages and should be employed whenever possible. Thus it affords a good exposure of the growth which if necessary can easily be destroyed by diathermy; it is easy to

insert the radium in such a manner that the whole region obtains uniform radiation; the opening in the lower part of the cavity affords free drainage and good inspection so that at any time an early recurrence can be detected; the opening can easily be blocked by a suitable denture, which can be removed for cleaning the cavity; there is less tendency to crusting than with other methods, and as a rule there is no external deformity.

*Rouge's operation.* An incision is made under the upper lip, and by turning up the nose and face access is obtained to the growth from in front. This method does not give nearly such good exposure or drainage as transpalatal, and has only rarely been employed.

*Moure's operation.* The incision is made by the side of the nose. When a transverse incision is also necessary it can be made along the conjunctiva of the lower eyelid, as suggested by TROTTER. By removing the anterior wall of the maxilla the growth can be exposed and treated with diathermy and radium. Although free exposure can be obtained this method produces more scarring and deformity, drainage is inadequate, troublesome crusting may supervene; and as there is no inspection-opening, early recurrences are difficult to detect. It is therefore employed only for growths which are situated high up in the ethmoidal and frontal regions.

*Implantation of needles.* To irradiate the nasal fossae and sinuses thoroughly without any cutting is a difficult procedure, but not impossible. In the nose, long needles — 4 to 6 cm. — are preferable. They can be inserted into the nose through the skin, just mesial to the edge of the pyriform opening of the bony nasal cavity, so that they lie horizontally and irradiate the cavity from the front almost to the back of the naso-pharynx (Figs. 1, 2). Five to seven needles lying one above the other can be inserted into each side. Needles can also be inserted into the antrum either obliquely through the outer wall of the nasal fossa or under the upper lip through the incisor fossa. In the case of ethmoidal growths it is preferable to insert the needles partly in the nose, but also through the skin, so that they lie in a horse-shoe arrangement along the inner wall of the orbit. As a rule it is advisable to supplement this treatment with X-rays.

The method has been adopted successfully in a good many cases where the growths had involved both sides of the nose or the base of the skull and were considered inoperable.

When the post-nasal space is involved by the growth, a tube, containing 50 to 100 mg. of radium with a 2 mm. platinum filter, is wrapped in enough gauze to fill the space completely and drawn up above the palate by a silk passed through the nose and anchored outside the nostril. Such a tube can be retained for 24 to 48 hours. Longer



Fig. 1.



Fig. 2.

Radiogram showing long needles in nasal fossae.

periods can be achieved by the use of 1 mg. needles enclosed in a gold filter of 1 mm. thickness for 24 to 48 hours.

#### Results

In considering results the importance of early diagnosis cannot be too strongly emphasized. Before the introduction of radium, even localized growths often recurred rapidly in spite of extensive excisions, because the wounds became re-infected at the time of the operation. With radium, this accident is not so likely to occur. The operation mortality has also been reduced owing to the fact that with radium there is less bleeding and less tendency to infection of the lower air passages than with other operations. The results that have been obtained have varied considerably with the different types of disease.

*Sarcoma.* The treatment that has been adopted depends on the type of the disease. In rapidly growing forms, such as round-celled, melanotic or spindle-celled growths, radium needles or tubes supplemented by deep X-rays without any cutting operation have given the best results. In most cases the growths have disappeared rapidly, leaving perfectly normal tissues. But in some of them after a period of a year to eighteen months local recurrences or metastases have formed in other parts of the body, causing fatal results in all of them. Of the seven cases treated

Table 1.

Sarcoma. Type	Situation	Alive (Years)	Dead (After years)
1. Melanotic . . . . .	Nasal fossa	—	1½
2. " . . . . .	Palate	—	1
3. Round-celled . . . . .	Nasopharynx	7	—
4. " . . . . .	Nasal fossa	—	?
5. " . . . . .	" "	—	¾
6. " . . . . .	" "	—	2
7. Spindle-celled . . . . .	" "	4	—
8. Angeio . . . . .	" "	—	?
9. Myxo . . . . .	Palate	—	?
10. Chondro . . . . .	Nasal fossa	6	—
11. Fibro . . . . .	" "	5	—
12. " . . . . .	" "	8	—
13. Myelo . . . . .	Palate	3	—
Cases 13.		6	7

in this group two have lived for periods of four to ten years and five have died within two years.

In slowly growing tumours it is probably better to explore the growth freely, to remove the greater part by diathermy and then to treat the cavity with radium. Of six of our cases treated in this manner, four have remained free from disease for periods of from three to eight years.

It will be noted, therefore, that in a series of thirteen cases of sarcoma treated by these means, six have lived for long periods. These results are surprising when one considers that in many of them the growths were extensive and that one is dealing with types which were not easily cured by surgical operations alone.

*Endothelioma.* As is well known, this type of growth shows an inveterate tendency to recur after simple removal in spite of the fact that it is often completely encapsulated. There is evidence to show that this result is not so likely to occur if radium or X-rays is employed. Whenever possible the growth should be removed freely either by shelling it out, or better by diathermy, and the wound afterwards treated with vigorous rays, either radium or X-rays.

Thirteen cases have been treated on these lines and of these, two are living for more than five years, and eleven have died after periods shown in Table 2. There is no doubt that in many of the fatal results great benefit was derived from the treatment, as not only were their

Table 2.

Endothelioma (Situation of origin)	Alive (years)	Dead (after years)
1. Nasal fossa . . . . .	—	1 <sup>1</sup>
2. > > . . . . .	—	2
3. > > . . . . .	—	1/4
4. > > . . . . .	—	2
5. > > . . . . .	5	—
6. > > . . . . .	—	1
7. Maxilla . . . . .	—	2 <sup>1</sup> / <sub>2</sub>
8. > . . . . .	—	5
9. > . . . . .	—	7
10. > . . . . .	7	—
11. > . . . . .	—	1/2
12. Orbit . . . . .	—	1/4
13. > . . . . .	—	1 <sup>1</sup> / <sub>2</sub>
Total Cases 13.	2	11

lives prolonged but they were also relieved temporarily of much of their distress.

*Carcinoma.* To cure this type of growth once it has invaded the bones is still a matter of great difficulty, and the results that we have obtained do not compare favourably with those of sarcoma and endothelioma; nor are they as good as the results published by the Mayo Clinic. Thirty-four cases have been treated; in most of them the growths originated in the sinuses or nasal fossae, but the list also includes those which started in the palate or in the post-nasal space and afterwards involved the nose. As a rule the greater part of the growth has been destroyed by diathermy before giving ray treatment, and this is probably the best method, excepting in those cases where the growths are so extensive as to be quite inoperable. In nearly all the cases temporary improvement has been noted, bleeding has ceased, discharge has been reduced, and pain has been relieved. But early recurrences have been the rule, largely because the growths were so extensive before treatment was commenced. Probably it will be found necessary to treat these growths with general, as well as local, ray treatment to prevent the frequent recurrences.

Of the 34 cases, only eight are alive for periods of from a half to six years. The remaining twenty-six have died, most of them within a year of treatment.

<sup>1</sup> This patient had multiple metastases under skin.

These results are disappointing, and at first sight are no better than those that followed simpler operations without radium. To some extent they can be explained by the fact that most of them were truly inoperable and could not have been treated at all by any other means. With better technique there seems no doubt that radium properly applied will give us better results.

Table 3.

## Carcinoma of Nasal Fossae

Alive over 6 years . . . . .	1	Dead after 4 years . . . . .	2
> > 4 > . . . . .	1	> > 2 > . . . . .	2
> > 2 > . . . . .	2	> > 1 > . . . . .	8
> > 1 > . . . . .	2	> less than 1 year . . . . .	14
> > 3/2 > . . . . .	2		
Total Cases 34.	8		26

## Malignant Growths of the Tonsil and Neighbourhood

In this series are included the growths that originated in the pharynx and involved either the tonsil, the posterior third of the tongue, the floor of the mouth far back, the palate, the jaws, or the post-nasal space. With a few exceptions where the primary growths were very small and localized these patients all had extensive disease in the glands of the neck. Most of them were inoperable. About one third of them were suffering from recurrences after previous operations. Thirty-three had epitheliomas, three sarcomas, and seven endotheliomas.

## Methods Employed

Various methods of treatment have been employed:

*Needles.* From 8 to 12 one mg. needles are inserted into and around the growth and are retained for 8 to 10 days. Whenever possible they should be placed around the growth rather than into it. To obtain a good result there seems no doubt that the barrage must be made at a considerable distance from as well as close to the growth. If the needles are inserted in pairs and their strings tied together as shown in the diagram (fig. 3), they rarely slip out of place or cause serious discomfort.

*Seeds.* Radon seeds of from 2 to 3 mc. starting strength have been used frequently and have certain advantages, chiefly that they are easy to implant and to retain. Also they cause less discomfort than needles. They should be buried around the growth taking care to space them accurately so that they lie about 1 cm. apart. Generally they are re-

tained for about ten days, after which as many as possible are removed, because in the pharynx a retained seed may cause irritation, sepsis, and pain.

*Treatment of neck.* In all cases whether enlarged glands can be felt or not it is advisable to treat the neck early by one or more of the following methods:

*Operation.* If the glands are localized in the tonsillar region and near the bifurcation of the carotid artery, the question of removal should always be considered. As a rule only the affected side should be treated and part or the whole of the sterno-mastoid muscle should be removed. In all these cases the patients should also receive full treatment with radium or X-rays.

If the glands are extensively involved and extend low down towards the clavicles, especially if they are very adherent to other structures, no operation should be attempted.

*Needling through skin.* This method is fully described elsewhere by Prof. GASK (see page 403). As it has only been tried by us for a short period it is difficult to judge its merits, but at first sight it appears to be the best method of giving a really adequate ray treatment for these cases.

*Collars.* Doubtless it is possible to give a good uniform irradiation to all the glands by this method. But although good results have been obtained by many workers, our personal observations are unsatisfactory and the benefit that has been obtained is only temporary. So far we have had no opportunity of using bomb treatments.

*X-rays.* Heavily filtered X-rays can certainly give good temporary results in these conditions, especially in the highly malignant types such as round celled sarcoma. At present it is very difficult to decide which is the best method of treating the neck, and each case must be considered on its merits.

#### Results

For some unexplained reason malignant growths in the region of the fauces appear to be almost always incurable. This is certainly the case

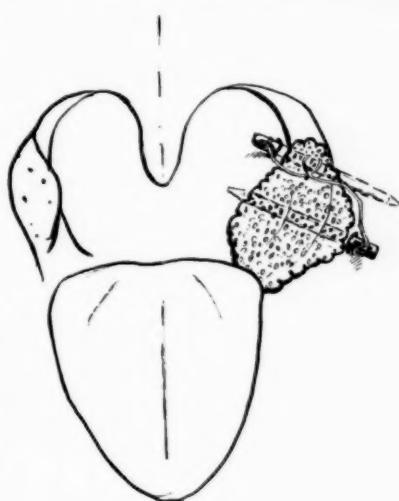


Fig. 3.

with surgery alone, and many of us feel this so strongly that we are agreed that such growths should never be removed with the knife. The question that can fairly be put is whether better results can be obtained by radium? Evidence is gradually accumulating to show that with better technique certain types of these growths can be cured. Thus sarcoma: there are three cases successfully treated by the above means that have lived for long periods and are apparently cured.

A young woman who had a round-celled sarcoma causing a massive tumour of the tonsil and numerous large glands in the neck was treated first by 100 mg. of radium buried in the neck and later by X-rays. At the operation a gland was removed for examination and submitted to Prof. ANDREWS who reported that the growth was a sarcoma of such high malignancy that he doubted if any treatment would be of the least value to her. After treatment all traces of her disease disappeared and she has remained well for nine years.

A man aged 42 had a fibro-sarcoma removed from his pharynx and some enlarged glands dissected out of his neck. Six months later there was extensive recurrence in the glands. With a long incision the whole neck was opened so that the glands were freely exposed. Twenty seven 1 mg. radium needles with 0.5 mm. filters were uniformly distributed all over his neck and retained for a week. Later he received X-ray treatment. All signs of his growth disappeared and he has remained well for five years.

A young woman had a spindle sarcoma involving the tonsil and pharynx. After treatment with radium, in spite of a severe secondary haemorrhage, the growth entirely disappeared and she has remained well for eight years.

In considering the treatment of round-celled sarcomas it must be remembered that they can be treated so well by X-rays alone that radium is often unnecessary.

*Endothelioma.* The position as regards endothelioma is very similar to that of sarcoma. Early growths that are completely encapsulated can easily be removed by enucleation and in a fair proportion of cases there is no recurrence, at any rate for many years. It seems possible that the percentage of cures can be increased by treating these cases with rays. We have here an instance of a type of growth for which combined surgery and rays give the best results. When the tumour can easily be enucleated it is better to get rid of it and then to treat the region either with radium or X-rays.

Surgery should not be attempted if the growth has extended into the neck or involved the Parotid gland. Of seven cases that have been successfully treated with radium and X-rays four have lived for periods of from one to nine years. (See table.)

**Endothelioma**

	Alive after (years)	Died after (years)
Fauces . . . . .	5	—
Fauces and Parotid . . . . .	3	—
"    "    "	9	—
"    "    "	—	few months
Fauces . . . . .	—	1½
Fauces and Parotid . . . . .	1	—
Fauces . . . . .	—	5
Cases 7.	4	3

*Carcinoma.* This is still the worst type of malignant disease of the fauces and up to the present radium treatment has failed to produce permanent cures. In early cases buried radium has often caused complete disappearance of the growths, but in most of them there has been a tendency to early recurrence and to dissemination in the glands of the neck. It would appear, therefore, that local treatment alone is of no value. In advanced cases radium is still less successful. Although a growth may shrink considerably and pain and discharge may be relieved temporarily, there seems to be an inveterate tendency to early recurrence. Thus, in a series of thirty-three cases which have been treated by various methods, twenty-one have died within a year and eight within two years. Only four are still living for periods up to 1½ years and none of them can be regarded at present as permanently relieved.

The only really good result that we have obtained with this type of growth was that of a man aged fifty who had an epithelioma involving the tonsil and pillars of the fauces with enlarged glands in the neck. The growth in the pharynx was excised freely by diathermy and the glands of the neck were afterwards removed *en bloc* together with the greater part of his sterno-mastoid muscle. Before and after the operations he was treated by X-rays. The growth entirely disappeared and he has remained well for nearly nine years.

These results are discouraging, but they are partly due to faulty technique. Although it has not been possible to prolong life, the treatment has certainly given temporary relief as regards pain and swallowing to many of the patients. With better technique one is hopeful of better results.

**Intrinsic Carcinoma of the Larynx**

Researches in the treatment of this type of growth by radium have been carried out in our department since 1913. At first radium was

used only for those growths which were so extensive as to be considered inoperable, as it was realized that localized growths could be treated by laryngo-fissure. Five years ago an operation was devised by two of us<sup>1</sup> closely resembling that of Dr. LEDOUX<sup>2</sup> working at Professor BAYET's clinic in Brussels.

#### Method Employed

A skin incision is made over the thyroid cartilage, either across the cartilage making a collar or starting at the centre of the hyoid bone and curving outwards and downwards along the posterior border. The infra-hyoid muscles are exposed and split longitudinally. The lateral aspect of the thyroid cartilage having been exposed, the perichondrium covering it is divided with a cross shaped incision and stripped freely. The greater part of the cartilage is resected so that a large window is made leaving nothing but a framework consisting of the four margins. By this means the outer surface of the growth covered by the perichondrium is exposed. It is very important not to destroy this capsule or to cut into the growth. From five to ten needles containing 1 mg. of radium with filters of 0.5 mm. of platinum or thicker are inserted vertically parallel to one another. To keep them in position the ends of the needles are inserted under the framework of the cartilage. Care is taken that the needles do not penetrate into the growth or into the air-passages. At the lower end, if the growth is subglottic, the needles are inserted either inside or outside the cricoid ring, but here the tissues are often so thin that unless care is taken the needles may perforate the air passage.

Each needle has attached to it a piece of linen thread soaked in a solution of flavine 1 in 1,000. All the threads are tied together and buried beneath the muscles. Double sutures are inserted into the skin, half of them being tied at once to close the wound completely and the other half left so that they can be tied later after the radium has been removed. No drainage is employed. When the growth has extended across the middle line, a second window is made on the opposite side and needles are buried there also. If the glottis is narrow and inadequate a low tracheotomy is then performed. Whenever possible this should be the last step of the operation so as to prevent infection of the laryngeal wound. In very early cases when the affected cord is freely movable and the glottis is widely open, it may not be necessary to insert a tracheotomy tube, but the risk of swelling owing to radium reaction must always be

<sup>1</sup> FINZI, N. S. and HARMER, DOUGLAS, Brit. Med. Journ. Nov. 17. 1928. Radium treatment of Intrinsic Carcinoma of the Larynx.

<sup>2</sup> LEDOUX, Drh de Cauel 1924, P. 100. Traitement Curvie-chronical du Cancer Laryngé.

remembered. Up to the present only one patient has required a late tracheotomy for the relief of laryngeal obstruction.

The needles have been left *in situ* for periods of from four and a half to eight days according to the number employed, the filtration, and the extent of the growth that had been treated. At the end of the period the wound generally contains considerable exudation which may be serous, blood-stained, or in a few cases purulent. Slight rise of temperature, 99° to 100°, can be expected especially when cough is troublesome. The amount of local inflammation varies considerably but in no case has it extended downwards and caused bronchitis. Although the treatment has been used for many patients who were seriously ill, no shock has resulted from it with one exception where the patient succumbed from the general anaesthetic. There has been practically no pain or discomfort and the patients have not been seriously ill.

In favourable cases changes in the growth occur rapidly; even in ten days the lesion may shrink greatly and become less nodular. An early improvement is a favourable sign. Later when the inflammation has subsided, in about six weeks, all signs of the growth may have disappeared leaving the cords unscarred, symmetrical and equally movable. About this period the tracheotomy tube can usually be removed.

#### Results

Twenty-three cases have now been treated, including six that were operated upon by other surgeons by this method. They can be grouped in three classes, namely — 1) Early cases in which the growth was strictly confined to one vocal cord and did not seriously involve either the anterior commissure or the arytenoid cartilage — namely, cases

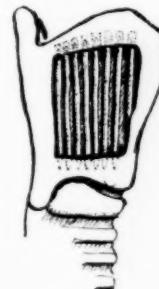


Fig. 4.



Fig. 5. Radiogram showing needles in Larynx

## Early Cases

No.	Operation (date)	Surgeon.	Alive after (years)	Dead after (years)	Larynx.	Voice.	Cause of Death
1	1925 . . . . .	Harmer	—	2	—	—	Heart failure
2	» . . . . .	»	4	—	Normal	Strong	—
3	» . . . . .	—	3½	—	»	Normal	—
4	» . . . . .	Rose	3½	—	»	»	—
5	1926 . . . . .	Harmer	2½	—	»	Hoarse	—
6	1927 . . . . .	»	2¼	—	»	Normal	—
7	1928 . . . . .	»	1¾	—	»	»	—
8	» . . . . .	»	1½	—	»	»	—
9	» . . . . .	Yates	—	10 days	—	—	Influenza
10	1929 . . . . .	Mollison	5/12	—	Improved	Hoarse	—
11	» . . . . .	»	5/12	—	»	»	—
12	» . . . . .	Ibbotson	4/12	—	Normal	Normal	—
13	» . . . . .	Harmer	4/12	—	No improvement	—	—
14	» . . . . .	Cade	1/12	—	Early improvement	—	—
Cases 14.		—	12	2	—	—	—

that could have been treated by laryngo-fissure. — In this class there were 14 cases. In 8 the growths have entirely disappeared, the patients remaining well for periods of from one to four years. The affected vocal cords have become freely movable even in those patients where there was complete fixation previously. In some of them the cords have recovered to such an extent that it is now difficult to say on which side the growth was situated. The results are far superior to anything obtained by surgery particularly as regards the voices, the worst voice being better than the average obtained by laryngo-fissure and the best absolutely normal. There seems to be no doubt that in early cases a high percentage of cures can be expected, and the after-results are superior to those that have been obtained by operation.

2) Advanced cases in which the disease was intrinsic but had crossed the middle line in front and involved the other vocal cord to such an extent that they could only have been cured by some form of laryngectomy. — There are six cases in this class. One of them has been cured for five years; in another the disease entirely disappeared and the voice became normal again, but a year later a recurrence formed in his tracheotomy wound which was inoperable, causing a fatal result eight months later. In one case the growth shrank leaving fibrous stenosis in the larynx, and later on there was a recurrence which ended fatally. In three

## Advanced Cases

No.	Operation (date)	Surgeon.	Alive after (years)	Dead after (years)	Larynx.	Voice.	Cause of death
1	1924 . . . .	Harmer	5	—	Normal	Good	—
2	» . . . .	»	—	1 <sup>3</sup> / <sub>4</sub>	Stenosis	Husky	Bronchitis
3	» . . . .	»	—	1 <sup>8</sup> / <sub>12</sub>	Normal	Normal	Recurrence in trachea
4	1925 . . . .	»	—	2	Stenosis	Husky	Debility
5	» . . . .	»	—	3 <sup>8</sup> / <sub>12</sub>	Normal	Normal	Recurrence in Larynx
6	» . . . .	»	—	1 <sup>2</sup> / <sub>12</sub>	No improvement		Debility
7	1927 . . . .	»	—	9/ <sub>12</sub>	Normal	Normal	Haematemesis
8	» . . . .	»	1 <sup>1</sup> / <sub>2</sub>	—	No improvement		—
9	1928 . . . .	Rose	—	2 <sup>1</sup> / <sub>2</sub>	No improvement		Paralysis agitans
Cases 9.		—	2	7	—	—	—

cases no improvement was noticed. The voice-results in this group have been infinitely superior to anything which can be obtained by laryngectomy. Many patients will even prefer an increased risk to life rather than lose their voices. As far as our evidence goes radium treatment does not increase this risk and when such small doses have been used there is no contra-indication to laryngectomy being performed later. Probably a rule should be made that if radium does not give immediate relief so that the growth has entirely disappeared within three months, laryngectomy should then be performed.

3) Inoperable cases in which the disease has extended into the pharynx or through the cartilages with enlargement of the cervical glands. It is always doubtful whether this type should be treated by buried radium or not, but each case should be considered on its merits. If radium is used needles must be buried in the larynx and in the neck as described elsewhere. In one case of this type the growth entirely disappeared after radium, and the glands which contained carcinoma were removed by operation. The larynx remained healthy for 2<sup>1</sup>/<sub>2</sub> years and the voice practically normal. Afterwards a recurrence occurred and he died nearly four years after his first treatment.

The value of heavily filtered deep X-rays should also be mentioned. The results are certainly encouraging. At present it is early to be certain to what extent the cures are permanent. It is possible that buried radium will be found to be the best method of treatment for all cases of intrinsic carcinoma of the larynx. As already mentioned a high percent-

age of cures can be obtained in early cases and so far there is no evidence that there is any danger of dissemination after this treatment if it is properly applied.

For advanced cases radium should always be tried before laryngectomy and if the disease is not completely eradicated the larynx can be removed later. The only serious complication which has been met with after this treatment is perichondritis which has resulted from over-dosage. Two instances of this have been seen in patients treated elsewhere and extensive thickening of the whole larynx resulted with great tenderness, abscess-formation, and pain. In one of the patients the pain had been constant since the operation. Obviously, therefore, it is important to avoid this accident of over-dosage, because once sepsis supervenes after radium has been used the patient is certain to suffer greatly and it may be impossible to relieve the pain. In our series no patient has been made worse by the treatment. A high percentage have obtained the greatest relief.

Reviewing the 127 cases tabulated above it will be seen that 39 are living for periods of from one to nine years and that 20 of these have lived for over three years free from disease. The reason that no case is known to have been cured for more than nine years is because radium was at first only employed for very advanced cases, because the supply of radium was inadequate, and because we did not know how to use it. Great progress has been made in the last five years, but the treatment is still so complicated that it can only be successful if it is carried out by surgeons working in close co-operation with radium specialists.

In many instances good results can only be obtained by combining surgery — for preference, diathermy — with radium or with X-rays.

The response to radium depends partly on the nature of the growth but still more upon the region affected. Carcinomas in the larynx appear to be particularly susceptible to radium. In the nose they are more difficult to cure because they are generally advanced and the bones are so readily invaded. At present we have no satisfactory method of treating carcinoma in the region of the fauces, largely owing to early dissemination in the glands of the neck.

Sarcomas both in the nose and in the pharynx are particularly sensitive to radium. Far better results can be obtained by ray treatments than by surgery. This rule also applies to endotheliomas.

Although the percentage of cures is not high, it must be remembered that we are dealing with very virulent types of growths in which surgery alone gives poor results; that radium can often give temporary relief to patients suffering from inoperable disease; that in some cases which are inoperable it may be possible to excise the growth successfully by

diathermy after it has been localized by radium; that it often prolongs life.

Lastly, the importance of early diagnosis cannot be too strongly emphasized. The earlier the disease the more favourable it is for radium treatment.

### SUMMARY

The authors after 15 years' experience are of the opinion that radium alone, or radium combined with surgery, gives better results in malignant disease of the upper air passages than surgery alone. Implantation of radium needles for a long period is used whenever possible. Malignant growth of the nasal fossae or accessory sinus are approached in various ways, usually transpalatal. The results in sarcomatous growths have been good, 6 of 13 patients having remained alive for periods of 3 to 8 years. The results with endothelioma have been worse, only 2 of 13 patients having survived more than five years. Of 34 cases of carcinoma, 8 have survived for periods of 6 months to 6 years; nearly all of these were inoperable. Malignant growths of the tonsil and neighbourhood have been treated with buried radium needles. Improvement has been obtained, but very few patients have been cured. Intrinsic carcinoma of the larynx has been treated by implanting radium needles through a window in the thyroid cartilage. The results have been very good in 12 of 14 early cases, and in 2 of 9 advanced cases.

### ZUSAMMENFASSUNG

Die Verff. sind nach 15jähriger Erfahrung der Ansicht, dass Radiumbehandlung allein oder mit einem chirurgischen Eingriff kombiniert, bei malignen Leiden der oberen Luftwege bessere Resultate gibt als Operation allein. Wenn irgendmöglich, wird eine Implantation von Radiumnadeln für eine lange Periode gemacht. Maligne Geschwülste der Nasen- oder Nebenhöhlen werden auf verschiedenen Wegen angegriffen, gewöhnlich transpalatal. Bei sarkomatösen Geschwüsten waren die Resultate gut, 6 von 13 Patienten blieben für einen Zeitraum von 3—8 Jahren am Leben. Bei Endotheliom waren die Resultate schlechter; nur 2 von 13 Patienten überlebten einen Zeitraum von fünf Jahren. Von 34 Karzinomfällen waren 8 nach Perioden von 6 Monaten bis zu 6 Jahren noch am Leben; diese Fälle waren fast alle inoperabel. Maligne Geschwülste an den Tonsillen und in ihrer Umgebung wurden mit versenkten Radiumnadeln behandelt. Es wurden Besserungen erhalten, aber nur sehr wenige Patienten geheilt. Auf den Larynx beschränkte Karzinome wurden durch Implantierung von Radiumnadeln durch ein Fenster im Schildknorpel behandelt. In 12 von 14 frühen Fällen und in 2 von 9 vorgeschrittenen Fällen waren die Resultate sehr gut.

### RÉSUMÉ

Au bout d'une expérience datant de 15 ans, les auteurs ont acquis la conviction que le traitement par le radium seul ou combiné avec un traitement opératoire donne de meilleurs résultats dans les affections malignes des voies respiratoires.

ratoires supérieures que le traitement opératoire seul. Ils recourent, dans la plus large mesure possible à l'implantation d'aiguilles laissées en place pendant une longue période. Les affections malignes des fosses nasales et des sinus sont abordées par diverses voies, le plus souvent par la voie transpalatine. Les résultats obtenus dans les tumeurs sarcomateuses ont été bons: 6 malades sur 13 ont survécu pendant une période variant de 3 à 8 ans. Les résultats sont moins bons dans l'épithélioma: 2 survies supérieures à 5 ans sur 13 malades. Sur 34 cas de carcinome, 8 ont survécu pendant un délai variant de 6 mois à 6 ans; presque tous étaient inopérables. Les tumeurs des amygdales et de la région amygdalienne ont été traitées par l'implantation d'aiguilles de radium. On a obtenu une amélioration, mais très peu de guérisons. Le cancer propre du larynx a été traité par l'implantation d'aiguilles de radium à travers une fenêtre pratiquée dans le cartilage thyroïde. Les résultats ont été très bons dans 12 des 14 cas graves et dans 2 des 9 cas avancés.

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## RADIOLOGICAL WORK IN THE GYNAECOLOGICAL DEPARTMENT, ST. BARTHOLOMEW'S HOSPITAL

by

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Before the year 1921 a few cases of carcinoma of the cervix were treated with radiotherapy by the late Dr. WILLIAMSON and Dr. FINZI and although there are no very accurate records of the number, it is known that some are living to the present day.

In 1921 the Hospital was lent 150 mg. of radium element by the Medical Research Council, and this was allotted to the Gynaecological Department two days a week. The fact that the radium was in the form of two tubes of 50 mg. of radium element each, and 13 needles containing in all 62 mg. of the element influenced the technique in the first cases treated. At that time most of the literature seemed to be somewhat vague as to the best method to be adopted, and it was therefore decided to treat the patients with 100 mg. of radium element into the cervical canal and the 13 needles implanted in the fornices. These needles had a filter of 0.4 mm. of platinum and were about 23.5 mm. long.

At first the radium was left in for 8 hours at a time and the application repeated on three occasions at intervals of a month. Sections were taken before and after each application. By this method there seemed to be very little evidence of change microscopically and macroscopically, and the technique was therefore abandoned.

The radium was next left in situ for 24 hours on each occasion and this produced a very much better immediate result. The question then arose as to whether the improvement was due to the increase in the total

dosage or to the increase in the time element. It was considered that the increased time factor was responsible, and from that day until the present time the tendency has been to increase the duration of exposure and to diminish the intensity.

When a series was undertaken, using 50 mg. of radium element contained in about 22 needles and left in position for 144 hours, there is little doubt that the immediate results — as judged by the disappearance of growth microscopically and macroscopically, cessation of haemorrhage, etc. — were very much more encouraging. It may be mentioned that this same principle of a small intensity and a long time factor has been adopted in other departments of the hospital also with more promising results. The gynaecological condition in which this difference is most obvious is that of carcinoma of the vulva. Although the number of such cases so far treated is small, yet this very resistant type of neoplasm has disappeared and healing has taken place, by using a small amount of radium, such as a total of 10 mg. of the element in 15 needles for 2—3 weeks.

The actual technique used for the vaginal application of radium in carcinoma of the cervix is as follows: The patient is taken into hospital and the growth cleaned to some extent by means of douches. Then the patient, under a general anaesthetic, is put in the lithotomy position and after a piece of the neoplasm has been removed for microscopic examination, 20 to 25 needles are inserted in and around the growth. The majority of these needles contain 2 mgrms. of radium element. Their active length is 3.2 cm., the thickness of the walls is 0.5 mm. of platinum. After the insertion of the needles the whole vagina is carefully plugged with gauze wrung out in flavine of a strength of not more than one in 4,000 and left in position for six days.

It is necessary now to consider the advantages and disadvantages of this prolonged irradiation in cases of carcinoma of the cervix. There is no doubt that the reaction soon after the radium is removed is at times very severe. Proctitis may last several weeks, although as a rule there seems to be little or no effect. The bladder, on the other hand, does not appear to be so sensitive, and little inconvenience is caused. At a later date fibrosis around the cervix and in front of the rectum is noticeable in the majority of cases, which makes it extremely difficult to say whether the induration is merely fibrous tissue or consists of latent malignant cells. On the other hand the absence of recurrence *in situ* does suggest that as far as the cervix and vagina are concerned the increased duration of exposure is a very important factor.

Why is it that in malignant disease of the cervix there are so many failures in the more advanced cases? In many other diseases, such as streptococcal infection, we know there is a body resistance to the infect-

ion, and that once the body resistance begins to give out, the increase in the number of organisms and toxins proves to be rapidly fatal to the patient. Is there such a thing as a carcinoma resistance in a patient, and is it an essential factor in the successful treatment by radium therapy? It would seem that the Swedish school holds this idea and it is felt that any damage to normal tissues may materially diminish that cancer resistance. Hence the relatively small duration of exposure employed at Stockholm. If this principle is true it is difficult to account for the ease with which even in advanced cases the malignant cells in the cervix and vagina are destroyed and healing takes place.

At St. Bartholomew's the idea that insufficient irradiation of the deeper parts of the growth is the cause of failure has stimulated efforts to irradiate the glands and parametrium by other methods. For this purpose two series of cases are being treated:

1. With X-ray in addition to local application of radium.
2. Intra-abdominal radium in addition to the local application.

The first of these methods is being carried out by Dr. BARRIS and Dr. LEVITT, who report as follows:

#### **The Place of X-rays in the Treatment of malignant Disease of the Uterus**

In considering the place of X-rays in the treatment of malignant disease of the uterus, there are three distinct questions which have to be discussed, and will have to be answered before we can assign to this therapeutic agent its proper place in the scheme of treatment.

These questions are, firstly, what is the value of X-rays in the treatment of malignant disease of the uterus? Secondly, what is the value of X-rays when used in combination with radium? And thirdly, what is the value of X-rays when used in combination with surgery?

Of the latter method — X-rays in combination with surgery — we have had little experience, and in this paper we propose to confine ourselves to the first two.

It would appear at first sight to be a simple matter to set forth the data obtained from the treatment of cases by these two methods. The cases treated by X-rays only and those treated by X-rays in combination with radium could be placed in separate groups and the results obtained in each group reported separately, and compared. Unfortunately, however, the matter is not quite so simple as that, since there are many complicating circumstances. These arise from the fact that in many cases treated in the first instance by X-rays only, recurrences occurred, which, at a later date were treated with radium. The converse has also occurred, certain cases of recurrence after radium treatment having been treated by X-rays.

It is manifestly incorrect to place cases which were X-ray failures, so to speak, and were subsequently treated with radium, in the same group as cases in which combined X-ray and radium treatment was planned and carried out from the beginning. In the same way, it would not be correct to group cases of recurrence after radium treated by X-rays together with cases in which a planned combined treatment was carried out at first. Furthermore, in some of the cases in which planned combined treatment was applied, the X-rays preceded the radium, while in others it followed it. The question of sequence in combined treatments will be referred to later, when it will appear that it is advisable to keep the cases in which the X-rays preceded the radium, and those in which they followed it, in two separate groups.

We are thus obliged to divide the cases into five treatment groups, as follows:

- A. Cases treated by X-rays only.
- B. Cases originally in Group A, but in which the local result was unsatisfactory, or in which recurrence occurred and radium was subsequently applied.
- C. Cases treated by X-rays followed by radium in which this method of treatment was planned from the beginning.
- D. Cases treated by radium followed by X-rays in which this method of treatment was planned from the beginning.
- E. Cases with recurrences after radium treatment which were treated by X-rays,

Classifying the patients in accordance with these principles, the numbers and grouping of all the cases treated from the commencement of the X-ray research in November 1924 to December 1928 are shown below. For convenience in reporting, the cases treated in the last two months of 1924 are added to the 1925 cases.

**Number and Grouping of Cases Treated**

	Group A	Group B	Group C	Group D	Group E	Total
1924-25 . . . . .	4	0	1	4	3	12
1926 . . . . .	2	1	2	0	0	5
1927 . . . . .	3	3	3	1	0	10
1928 . . . . .	14	2	3	0	2	21

#### **Technique**

The radium technique was the same as that employed in the non-combined cases and described above. The X-ray technique was the in-

tensive split-dose technique described in another paper in this issue (FINZI and LEVITT).

No reduction in dosage, either of the X-rays or of the radium was found to be necessary.

### Results

A general view of the results obtained in malignant disease of the uterus is given in the following table.

*Note:* the letters N. A. D. mean alive, well and free from evidence of the disease at the time of writing (May 1929).

	Number treated	Now N. A. D.	Alive, disease present	Dead
1924—25 . . . . .	12	3	0	9
1926 . . . . .	5	2	1	2
1927 . . . . .	10	2	3	5
1928 . . . . .	21	8	11	2

The above results are set forth in detail in the next table.

### Tabular Summary of Results in all Cases Treated from 1924 to 1928

#### Explanation of abbreviations used in table

C of C means carcinoma of the uterine cervix.

C of B      "      "      "      body of the uterus.

S of V      "      "      "      sarcoma of the vulva.

Ch-ep.      "      chorion-epithelioma.

S of C      "      sarcoma of the cervix.

N. A. D. (nothing abnormal demonstrated) means alive, well and free from signs of the disease at the time of writing (May 1929).<sup>1</sup>

	Numbers and grouping of cases treated					Cases now N. A. D.					Alive, disease present	Dead
	A	B	C	D	E	A	B	C	D	E		
1924—25	C of C											
	2nd deg. . .	0	0	0	1	0	0	0	0	1	0	
	3rd deg. . .	0	0	0	3	0	0	0	0	0	0	{ none
	4th deg. . .	1	0	0	0	2	0	0	0	0	0	6
	C of B . . .	3	0	1	0	0	1	0	1	0	0	none
1926	S of V . . .	0	0	0	0	1	0	0	0	0	0	2
	C of C											
	3rd deg. . .	1	0	2	0	0	0	0	1	0	0	none
1926	C of B . . .	1	1	0	0	0	1	0	0	0	0	1
												0

<sup>1</sup> The letters A B C D E refer to the treatment groups described on Page 382.

		Numbers and grouping of cases treated					Cases now N. A. D.					Alive, disease present	Dead
		A	B	C	D	E	A	B	C	D	E		
1927	C of C	0	0	1	0	0	0	0	0	0	0	{	2
	2nd deg. . .	0	0	1	0	0	0	0	1	0	0		
	3rd deg. . .	1	1	2	1	0	0	0	0	0	0		
	4th deg. . .	2	0	0	0	0	0	0	0	0	0		
1928	C of B . . .	2	0	0	0	1	0	0	0	0	0	{	1
	C of C	3	0	0	0	0	3	0	9	0	0		
	2nd deg. . .	3	0	0	0	0	1	0	0	0	0		
	3rd deg. . .	6	2	0	0	0	1	0	0	0	0		
	4th deg. . .	4	0	1	0	2	1	0	0	0	0		
	C of B . . .	1	0	0	0	0	1	0	0	0	0		
	S of C . . .	0	0	1	0	0	0	0	1	0	0		
	Ch-ep. . . .	0	0	1	0	0	0	0	1	0	0		0

While it is manifestly impossible to draw any conclusions from this small series of cases, there are, nevertheless, certain interesting facts which emerge, and are worthy of further consideration.

In the first place, it will be seen that of six cases of carcinoma of the cervix (third and fourth degree) treated by X-rays only from 1924 to 1927, only one is alive, and none is free from signs of the disease at the present time. On the other hand, of eight cases treated by combined X-rays and radium, three are alive and well, and free from recurrence.

Secondly, in spite of the fact that full dosage both of radium and X-rays was applied, no ill effects of the combination were observed. Thus, while it is usually found that after radium needle treatment of carcinoma of the cervix, even when the result is satisfactory, some induration almost invariably remains in the pelvis, in the three successful cases referred to treated by combined methods, very little, if any induration can be felt. One would expect that the addition of the X-ray treatment to the radium treatment would tend to increase rather than to diminish this result. Fortunately, however, this is not the case.

Turning now to the results in cases of carcinoma corporis, five out of six cases treated are alive, and of these, four are well, free from recurrence — a striking contrast to the results obtained in the cervix cases.

Apart, however, from the numerical results, certain important facts have been noted in the course of following up these cases.

It was found, for instance, that the majority of cases in the X-ray only group, as a result of the X-ray treatment, became free from all symptoms and signs of the disease for a time, often for many months. In two cases in which combined treatment was planned, this disappearance of the symptoms and signs was so complete after the X-ray treatment that the radium treatment was considered unnecessary and was

not carried out. Sooner or later, however, the cervix cases recurred, and the recurrence was always local at first. After radium treatment, on the other hand, as has been emphasized above, local recurrence is the exception.

These facts are in favour of combining the X-ray and radium treatment. Furthermore, we have learnt that when recurrences occur after radium treatment, they occur peripherally in parts which are probably just outside the zone of fire of the radium, or perhaps where the intensity of the irradiation has been low.

Knowing as we do that considerable shrinking and even temporary complete disappearance of a carcinoma of the cervix can be brought about by X-rays, is it not possible that recurrence after radium would be rendered less frequent if the way were prepared for the radium by previous X-ray irradiation? In this way, the shrinking of the growth would tend to bring it more completely within the zone of fire, and the dosage in the peripheral zone of low intensity would be supplemented by the X-rays. On physical grounds also the two agents, X-rays and radium, are well suited for combination; indeed it might almost be said, from this point, that they are complementary agents.

Nor does there appear to be any disadvantages associated with the combination.

Two points, however, require consideration in connection with the combined methods of treatment. These are, firstly, the sequence of the application of the X-rays and radium respectively, and secondly, the interval which should elapse between the application of the two agents.

*Sequence.* There is as yet no evidence to show whether better results are obtained when the radium precedes or follows the X-ray treatment. The fact that recurrence after radium is rarely local would suggest that the radium is powerful enough to destroy the growth wherever a satisfactory intensity can be obtained, and as mentioned above, previous X-ray treatment would act by shrinking the growth and thus bringing it more completely within the range of the radium needles. This fact is in favour of the X-ray treatment preceding the radium.

It is with the object of elucidating this problem of sequence, that the cases treated by X-rays followed by radium and those treated by radium followed by X-rays are being kept in separate groups.

*Interval.* Here again, there is no definite indication. The interval in the small number of cases referred to above has not been uniform. It varied from a few days to several weeks. There has been no appreciable differences in the results which have been obtained.

In a general hospital where bed accommodation is limited, the difficulties in treating a large series of cases with a uniform interval are very great, in view of the impossibility of guaranteeing a bed for a patient

on a specified date. From this point of view, it might be easier to apply the radium at the termination of the X-ray treatment, while the patient is still in hospital.

It must be said, however, that on theoretical grounds, sufficient time ought to be allowed to elapse after the X-ray treatment and before the radium treatment to allow the maximum degree of shrinking to occur. This interval would appear to be about six weeks.

It is not for a moment suggested that on the very small amount of evidence available, one ought to conclude that combined X-ray and radium treatment is superior to treatment by either of these agents alone. It is submitted, however, that there is a good case for a thorough trial of the combination, in a sufficiently large number of cases.

#### **Intra-abdominal Radium in the Treatment of Malignant Disease of the Uterus**

The second of the two methods is carried out by Dr. DONALDSON, who reports as follows:

It is to the Brussels Radium Institute that we owe the first attempt along these lines. The technique they used in 1919 consisted in putting the patient in the Trendelenburg position, opening the abdomen, and when the posterior layer of the broad ligaments had been incised, placing 20 mgrms. of radium element in a single tube at the base of each ligament. In addition to this they sometimes put needles into the uterus. The sutures from these tubes were carried out through the lower end of the abdominal incision, and the whole pelvis packed with 6—8 yards of gauze. At the end of 4—5 days this was removed with or without an anaesthetic.

Dr. DONALDSON modified this technique by using needles instead of tubes. Thirteen cases were treated during 1923—24 with this technique.

Of these 13 cases, one was of the 1st degree and is living and well after 4 years.

4 were of the 2nd degree, and of the 4 cases two are living after 5 years, although the latest report from one is not very satisfactory. Two have died, one after 14 months and the other after seven months.

6 were of the 3rd degree and three of these six are living after 5 years or more, and three have died, having lived less than one year.

2 were of the 4th degree, one is living after 5 years and the other died after 1 year 10 months.

It will be seen, therefore, that of the 13 cases six are alive after five years, and one has lived for 4 years and shows no signs of the disease.

### Present Technique

The intra-abdominal insertion of radium is usually carried out about 6—8 weeks after the vaginal application — that is to say, when the local external growth has disappeared and all ulceration healed. No attempt so far has been made to make the intra-abdominal application at the same time as the vaginal, merely on the theoretical grounds that whilst there is an infected area in the cervix and fornices it is perhaps not wise to do anything to the abdomen and parametrium which might lower the resistance to that infection.

The patient is put into the Trendelenburg position and the abdomen opened, a general examination is made of the lower aortic glands, in addition to the pelvic organs and the iliac glands. The intestines are packed off and the uterus pulled forward; the parietal peritoneum is then picked up with forceps and the needle inserted, leaving only the eye of the needle protruding from the peritoneum. The suture is put through a small portion of the peritoneum below the level of the needle eye, and the knot tied over a green glass bead to prevent cutting through the thin peritoneal tissue, and also to help in finding the needles later.

The needles are placed at a distance of 1— $1\frac{1}{2}$  cm. from each other, starting at one sacro-iliac synchondrosis and ending at the corresponding joint of the opposite side. In addition four or possibly more needles are placed in front of the broad ligaments in the hope of eradicating the disease from the obturator glands. The end of the ligatures are tied together and pushed down into the pouch of Douglas. The abdomen is sewn up completely and the radium left in situ for seven days. At the end of this time the abdomen is again opened and the radium removed.

An objection to this technique is the second laparotomy at the end of a week, but up to the present it has been felt that in order to keep them in position the needles should be sutured to the peritoneum, which makes it impossible to pull them out. In addition to this they are often placed at an angle to the line of traction and damage might be done if pulled out blindly. DODD of the Westminster Hospital has modified this technique by using radium needles in catheters placed retro-peritoneally so that they can be withdrawn through stab incisions. In addition he combines this with excision of the glands.

### Immediate Results

The first case chosen in this series was a patient (2nd degree) in whom it was considered there was a reasonable chance of the treatment being of some value, and the operation took place in October 1927. Three or four months were allowed to elapse in order to see if there were any untoward symptoms before attempting the technique again. At the

end of this time the patient was found to be extremely well. During the year 1928 twelve other cases were treated in a similar manner. Of these 3 were diagnosed as being 1st degree, 2 were of the 2nd degree, 2 of the 3rd degree, and 5 were of the 4th degree.

Of the 1st degree cases there is little to be said except that on opening the abdomen one of these was found to have enlarged obturator glands. The operation was done in September 1928, but in December a letter stated that she did not feel very well and she died in Feb. 1929. Another, operated on in June, is very well at the present time. The third, operated on in July 1928 has vague pains but appears to be doing well.

The two cases diagnosed as second degree are both doing well.

Of the 3rd degree cases one, operated on in March, has died recently. This patient is of particular interest because when she had her vaginal application it was noticed that she had a swelling in the region of the right kidney. At the intra-abdominal operation it was found that this swelling was due to a hydro-nephrosis which seemed to be caused by the pressure of the growth round the ureter. In spite of this the patient wrote in December saying: »There is no doubt my health generally is greatly improved. I feed regularly and have regained much of my lost weight.»

Of the 4th degree cases, one had a slight degree of intestinal obstruction and masses of glands were found in the pelvis, and a colostomy was performed and radium inserted. She has since died; there is no evidence that the radium improved her condition.

Another late case was admitted in April, 1928, and was so anaemic that a blood transfusion was carried out before putting the radium in per vaginam. She had an ulcer of the cervix two inches in diameter, involving the fornices. Two months later the vagina had completely healed and an intra-abdominal operation was carried out. Near the aorta glands were found which felt hard and were probably malignant. In December there was marked induration in front of the rectum, but the patient was extremely well considering her original condition.

Another very advanced case was treated in May and was found to have pus in Douglas's pouch. Radium, however, was inserted and there is little doubt that this was an error of judgement, as in spite of drainage the patient got general peritonitis and died as a result of the operation.

The next case in this series was operated on in September and found to have large masses of glands, some as large as a walnut. It was realized that it was not possible to effect a cure, but it was thought that if those near the uterus were diminished in size it might reduce the amount of pain at a later date. The needles were therefore concentrated on those

glands. In December the mass of glands did not seem to be diminished and the patient was obviously not so well.

The last of the 4th degree cases was treated in December. Considerable adhesions were found in the pelvis, but no markedly enlarged glands. There was, however, much induration in both the broad ligaments. Following the removal of the radium there was a certain amount of wound infection, but this cleared up and the patient left hospital in fair condition.

It will be seen, therefore, that of the 13 cases 9 are living, but it is too early to say much about their condition.

#### Conclusions

Since it has been proved beyond doubt that radium will entirely eradicate carcinoma in the cervix and vagina it is logical to try and extend the influence of the radium to the growing edge of the tumour by means of intra-abdominal radium. The cases so far treated show that this method is not attended by any undue risk to the patient, and the small series treated in 1923—24 show sufficiently good results to justify us in investigating further this line of treatment.

#### Statistics

The statistics so far obtained in carcinoma of the cervix uteri treated by radium only, include many methods, but speaking broadly, the present technique of using 50 mg. of radium element in multiple needles for 144 hours has been almost exclusively used since the end of 1924, but in some cases the intra-abdominal insertion of radium has also been employed.

With such a comparatively small series of cases it would be impossible to compare this technique with that of other clinics.

#### Statistics of Patients Suffering from Carcinoma of the Cervix Treated by Radium Alone

Year	Cases Treated	Alive Dec. 1922	Alive Dec. 1923	Alive Dec. 1924	Alive Dec. 1925	Alive Dec. 1926	Alive Dec. 1927	Alive Dec. 1928
<i>1st stage</i>								
1921 . . . . .								
1922 . . . . .								
1923 . . . . .	2	—	—	1	1	1	1	1
1924 . . . . .	4	—	—	—	2	2	2	2
1925 . . . . .	4	—	—	—	—	3	3	3
1926 . . . . .	6	—	—	—	—	—	5	5
1927 . . . . .	3	—	—	—	—	—	—	2

Year	Cases Treated	Alive Dec. 1922	Alive Dec. 1923	Alive Dec. 1924	Alive Dec. 1925	Alive Dec. 1926	Alive Dec. 1927	Alive Dec. 1928
<i>2nd stage</i>								
1921	7	4	4	1	1	1	1	1
1922	6	—	—	—	—	—	—	—
1923	5	—	—	2	1	1	1	1
1924	11	—	—	—	4	4	2	2
1925	3	—	—	—	—	3	—	—
1926	5	—	—	—	—	—	3	—
1927	4	—	—	—	—	—	—	—
<i>3rd stage</i>								
1921	8	5	2	2	1	1	1	—
1922	8	—	—	—	—	—	—	—
1923	8	—	—	—	1	1	1	1
1924	13	—	—	—	5	4	4	4
1925	10	—	—	—	—	3	1	—
1926	13	—	—	—	—	—	6	3
1927	13	—	—	—	—	—	—	6
<i>4th stage</i>								
1921	3	—	—	—	—	—	—	—
1922	3	—	—	—	—	—	—	—
1923	2	—	—	—	—	—	—	—
1924	6	—	—	—	2	1	1	1
1925	11	—	—	—	—	2	4	3
1926	9	—	—	—	—	—	—	2
1927	9	—	—	—	—	—	—	—

### Carcinoma of the Body of the Uterus

Very few such cases have been treated by radium alone. In one or two cases 50 mg. of radium element have been applied in the body of the uterus for 144 hours, and the uterus excised a week later. Sections did not show any great microscopic evidence of change in the condition. On the other hand, in one patient in whom the general health did not permit of hysterectomy, the radium was left in situ for two weeks. This patient remains well without symptoms 18 months after the original treatment.

### Carcinoma of the Vulva

Treatment of this condition by radium has already been mentioned. The technique employed is to use extremely small intensity needles for 14—21 days. The results of such prolonged dosage are promising.

### Treatment of Non-malignant Gynaecological Conditions with Radium

The only non-malignant condition that is treated in any great number is irregular haemorrhage at the menopause. The results of using 50 mg. of radium element for 72 hours were found to be better than those where the radium was in position for 24 hours, and the disadvantage, i. e., slight vaginal discharge for a few weeks, is trivial. The number of young patients treated by radium for irregular bleeding is too small for comment. The dose in such cases has been restricted to 50 mg. for 24 hours. In cases of small fibroids in middle-aged patients the same technique is used to bring about an artificial menopause as in those patients where no fibroids are present.

### SUMMARY

The paper describes work that has been done during the past 8 years, chiefly on the treatment of carcinoma of the cervix. At first a large dose was used for a short period. Since 1924 a smaller dose, usually about 45 mgr., has been used, needles being buried around the growth and left in position for 6 days. In addition, patients are being treated by X-rays, and some with intra-abdominal radium. The details of the intra-abdominal method are described. Since 1921 a total of 202 patients have been treated. The local results have been uniformly good, and recurrences in the cervix are seldom seen. Those patients that die have metastatic growths in the iliac glands.

The treatment of other malignant conditions in gynaecology are briefly discussed. In cases of carcinoma of the vulva, the authors are using quite small intensities, such as 15 mg. distributed in 10 or more needles, kept in position from 2—3 weeks. The result of such treatment on the primary growth is remarkable, but sufficient time has not elapsed to say what the final results will be.

In the non-malignant conditions, such as menopausal haemorrhage and small fibroids, the authors consider that 50 mg. of radium used for 72 hours is more efficient than a larger dose used for 24 hours.

### ZUSAMMENFASSUNG

Die Verff. berichten über die Tätigkeit der letzten 8 Jahre, besonders in Bezug auf die Behandlung des Zervixkarzinoms. Anfangs wurde für eine kurze Periode eine grosse Dosis verwendet, seit dem Jahre 1924 eine geringere, gewöhnlich ungefähr 45 mg. wobei die Nadeln rund um die Geschwulst implantiert und 6 Tage in dieser Lage belassen wurden. Außerdem wurden die Patientinnen mit Röntgenstrahlen behandelt und einige intraabdominal mit Radium. Es folgt dann eine Schilderung der Einzelheiten der intraabdominalen Methode. Seit dem Jahre 1921 wurden insgesamt 202 Patientinnen behandelt. Die lokalen Resultate

waren durchwegs gut, und Rezidiven im Zervix traten selten auf. Fälle mit tödlichem Ausgang zeigten metastatische Geschwülste in den Iliacaldrüsen.

Die Behandlung anderer maligner gynäkologischer Zustände ist kurz erörtert. In Fällen von Vulvakarzinom verwenden die Verfasser ganz kleine Dosen, z. B. 15 mg, auf 10 oder mehr Nadeln verteilt, die 2—3 Wochen liegen gelassen werden. Das Resultat einer solchen Behandlung der primären Geschwulst ist bemerkenswert, die verflossene Zeit ist aber zu kurz, um ein Urteil über die endgültigen Resultate abgeben zu können.

Bei nicht malignen Zuständen, wie menopausale Hämorrhagie und kleine Fibroide halten Verff. 50 mg Radium durch 72 Stunden für wirksamer als eine grössere Dosis durch 24 Stunden.

### RÉSUMÉ

Le présent travail décrit les travaux effectués, au cours des 8 dernières années, plus particulièrement dans le traitement du cancer du col. On administrait au début de fortes doses pendant une courte période. Depuis 1924, on recourt à des doses plus faibles, généralement 45 mg. environ, les aiguilles ayant été placées autour de la tumeur, et laissées en place pendant 6 jours. Les malades ont en outre subi un traitement par les rayons X, et, pour certains d'entre eux, la radiumthérapie intra-abdominale. Les auteurs décrivent les détails de la méthode de radiumthérapie intra-abdominale. Depuis 1921, 202 malades ont été ainsi traités. Les résultats locaux ont été uniformément favorables et les récidives au niveau du col rares. Les malades ayant succombé présentaient des tumeurs métastatiques dans les ganglions du bassin.

Les auteurs discutent brièvement le traitement des autres affections gynécologiques. Dans les cas de cancer de la vulve, les auteurs recourent à des intensités très faibles, d'environ 15 mg., réparties en 10 aiguilles ou plus, laissées en place pendant 2 à 3 semaines. Ce traitement donne, en ce qui concerne la tumeur primitive, un résultat remarquable; mais le traitement est d'origine encore trop récente pour qu'il soit possible de se prononcer sur les résultats finaux.

Dans les affections non malignes, telles que les hémorragies de la ménopause et les petits fibromes, les auteurs considèrent que 50 mg. de radium appliqués pendant 72 heures sont plus efficaces que des doses plus fortes appliquées pendant 24 heures.

## THE TREATMENT OF PRIMARY CARCINOMA OF THE BREAST WITH RADIUM

by

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The treatment of primary carcinoma of the breast with radium has not progressed in most radiological clinics beyond the experimental stage and has seldom been used for any cases other than those regarded as too far advanced for treatment by operation. A somewhat different attitude has been gradually assumed during the past five years by the members of the Surgical Professorial Unit under Prof. G. E. GASK at St. Bartholomew's Hospital, and by myself, until at the present time we regard treatment by buried needles as preferable to operation.

As far as I am aware no systematic treatment of carcinoma of the breast with buried radium needles had been attempted before 1924 when the present investigation was begun. Some preliminary experience was gained during the years 1922—24 with the treatment of recurrences which had appeared after operation. It was shown that a nodule of carcinoma could be made to disappear by local treatment with buried radium, although this hardly ever prolonged the patient's life, the disease having already been disseminated to more distant parts. The first case of primary carcinoma of the breast was treated in August, 1924, and to the end of April, 1929, 90 patients had been treated.

The treatment depended from the start on the application of a relatively small dose of radium for a long time, but was at first somewhat tentative. The directions in which the technique of the treatment has developed have been as follows:

1) to distribute the dose in smaller units; 2) to prolong the time of exposure; 3) to increase the area treated; 4) to extend the routine treatment of the areas of lymphatic drainage until every accessible area was receiving what appeared to be an adequate dose.

At the present time the main principles of the treatment are as follows:

### Dosage.

*1) Amount:* a relatively small dose is given for a long period, but the size of the dose will vary greatly with the size of the growth to be irradiated. Any amount up to 100 mgr. Ra element may be needed, and this should be distributed in about 35 needles. The majority of these needles should contain 3 mgr. of radium distributed along an active length of 4.8 cm. A smaller number should contain 2 mgr. with an active length of about 3.0 cm.

The needles required will therefore be approximately as follows:

Number	Ra element content	Active length
25 . . . . .	3 mg.	4.8 cm.
10 . . . . .	2 mg.	3.0 cm.
Total = 95 mg.		

*2) Filtration:* the needles used hitherto have been made of platinum with a thickness of 0.5 mm. More complete filtration and additional strength may be obtained by using platinum with a thickness of 0.6 mm.

*3) Time:* the radium should be allowed to remain in position for a minimum period of 120 hours (5 days). The average period should be 168 hours (7 days). This may occasionally be increased to 240 hours (10 days) or even more when the tumour is very large.

### Distribution.

The radium should be so distributed as to irradiate effectively two main areas 1) the primary growth 2) the lymphatic drainage.

*1) The primary growth:* the longer needles should be inserted about 1.5 cm. apart so as to irradiate evenly the whole of the tumour and the breast tissue for a considerable distance wide of it. Most of the needles should be placed in a plane deep to the growth. This will usually be between the mammary gland and the pectoral muscle. If the area to be covered is wider than the length of the needles, some may be inserted from each side, so that they will overlap in the centre. Sometimes, if the growth be a large one, a second layer of needles may be inserted in a plane more superficial than the first and at right angles to it, so that a «grid» of needles is formed, which will give an even illumination to the tumour. It is important to irradiate the deep surface and the periphery of the tumour because these are the most active parts

of it. It is also desirable to treat the surrounding breast in order to destroy any carcinoma cells which may have permeated the lymphatic channels in it. The needles should not be placed nearer to the skin than is absolutely necessary, owing to the sensitivity of the skin to radium.

2) *The lymphatic drainage*, which may be divided into five separate areas:

a) 3 to 5 long needles should be put beneath the pectoralis major muscle to catch the main lymph channels draining the breast.

b) 3 to 5 long needles should be inserted into the axilla distributed on its various walls. They should converge towards the apex, so as to form a cone of rays. The needle on the outer wall should be kept strictly parallel to the axillary vessels so as to avoid damage to these.

c) Infraclavicular region: 2 or 3 shorter needles should be inserted immediately below the central third of the clavicle, and parallel to it. These should pierce the pectoral muscle, and should be as nearly as possible on the costo-coracoid membrane.

d) SuprACLAVICULAR region: 2 or 3 shorter needles should be inserted immediately above the central third of the clavicle, and parallel to it. These should lie deep to the deep cervical fascia and superficial veins, and should be in close proximity to the subclavian vein and brachial plexus.

e) 3 or 4 shorter needles should be inserted obliquely into the upper intercostal spaces, so as to lie near the internal mammary artery and lymph glands. The points of the needles should project beneath the edge of the sternum for a short distance into the anterior mediastinum. The lowest one may come into contact with the pleura and cause inflammation and pain unless care is exercised.

A typical distribution of needles is shown in the accompanying diagram.



Fig. 1.

Typical distribution of radium needles in carcinoma of the breast. The position of the growth is indicated by a dotted line.

### Additional Apparatus.

It is convenient to have three forms of introducer for placing the needles in position. Two of these are large forceps on the principle of the Spencer-Wells haemostat with grooves cut in the jaw so that the needles can be gripped without damage. One holds a needle in the line of the forceps, the other holds it at right angles. A third introducer may sometimes be useful when a needle has to be placed at some distance from the skin, or when the tissues are very tough. This is made on the principle of the trochar and cannula. The trochar is made to project more than the full length of the needle beyond the cannula. When the trochar is withdrawn the needle is pushed by a stile along the cannula and into the track made for it by the trochar.

### Details of Technique.

1. The patient is anaesthetised with gas and oxygen. It is seldom necessary to use any additional kind of anaesthetic.
2. The skin of the chest wall, axilla, and neck is thoroughly cleaned with ether. No other reagent is used in order to avoid damaging the gold soldering of the needles.
3. A series of puncture wounds are made in the skin round the site of the carcinoma with a narrow-bladed pointed scalpel. The Bard-Parker blade No. 11 is specially suitable for the purpose. These punctures are about 1.5 cm. apart and placed so that the needles can be distributed as already described.
4. Similar punctures are made for the insertion of the needles in the lymphatic areas as already detailed.
5. Before the needles are inserted each has a strand of thick salmon-gut threaded through the eye and knotted once. These are allowed to protrude from the punctures in the skin, and are knotted together in bunches, so that if a needle comes out of place it will remain attached to the others and not be lost. If an absorbant ligature material, such as Pagenstecher thread, be used, some suppuration is liable to occur in the stab wounds.
6. The skin is cleaned and the area under treatment is covered with gauze, which is secured in position by broad strips of adhesive rubber plaster, overlapping the gauze all round, and forming an additional safeguard against the loss of needles. Zinc oxide strapping will give rise to secondary radiations which may injure the skin.
7. The needles are allowed to remain in position for the specified period, and are then removed, again under gas and oxygen anaesthesia. The ends of the needles may become caught under the skin, and the

process may be very painful unless the patient is under the influence of gas. The extraction of the needles is often facilitated by using as a guide the end of an aneurysm needle.

#### After Treatment.

Usually no after-treatment is needed except a gauze dressing for a few days until the stab wounds have healed. Occasionally after a latent period of a few days the patient develops a superficial «burn» with a weeping surface. This may need dressing with vaseline ointment for some weeks. If the growth was a scirrhous carcinoma already ulcerated on the surface before treatment, sloughing may follow an adequate treatment with radium. This does not spread beyond the growth itself, but may take a long time to heal, and will therefore need to be kept clean with daily dressings.

#### Results.

a) *Primary growth:* The growth will begin to shrink immediately after the treatment has been completed, and the shrinkage will continue, until at the end of two to three months a small tumour will have completely disappeared. If the tumour was large, shrinkage may go on for four months, but at the end of that time it may appear stationary. The residual tumour may consist only of the fibrous tissue which formed the matrix of the carcinoma, or it may contain some apparently active carcinoma cells. Two courses are then open: 1) to give a second treatment with radium; occasionally even a third may be called for some months later. 2) Or the residual tumour may be excised locally. No extensive operation is ever necessary. Experience and individual circumstances will determine which course is to be taken.

b) *Lymphatic glands:* In the majority of the patients treated, the only enlarged glands that were detected were in the axilla, the rest of the treatment given to lymphatic areas having been prophylactic. The effect on the enlarged glands has been very satisfactory. Usually they have disappeared entirely, even when they had been very large, leaving no trace, or only a slight thickening where they had been. Recurrences in the areas treated prophylactically have been very uncommon, though in a few cases a second treatment for enlargement of the glands has been given. The intercostal spaces have been irradiated only in the more recent cases.

#### Histological Evidence.

It was recognized that while this form of treatment was under trial it was necessary to obtain a histological proof of the nature of the tu-

mour. In the first fifty cases therefore of the present series, a small piece of the growth was taken for section when the needles were removed. This was done after irradiation rather than before in the belief that implantation of the growth in the incision was less likely to occur. On several occasions, however, this has resulted in the appearance of a small nodule of growth in the scar and a second treatment has been necessary to dispose of it. It became clear therefore, that a routine biopsy was contrary to the patient's interests, and after a positive result in fifty consecutive cases the practice has been abandoned. In the great majority of patients the clinical signs are sufficiently clear, and if any doubt as to the diagnosis remained it has been duly recorded.

If the response to irradiation seemed to be satisfactory, no surgical operation was performed. In a few instances excision of the area treated was carried out. In the two patients first treated, although great improvement had resulted, the area treated was excised in order to obtain information. Both specimens were found still to contain some carcinoma cells, but both had received what I should now regard as an inadequate dose. In spite of this, one of the patients is still quite well after the lapse of nearly five years. The other has died with recurrences. In a patient treated somewhat later in the series (No. 4), a massive growth was excised five and a half months after treatment of its deep surface with radium. Sections of the irradiated surface of the growth showed that very few carcinoma cells remained in this part, though there was more carcinoma still active at a greater distance from the radium. The tissues must necessarily protect those cells which are on that side of the tumour most distant from the radium, and it is not always possible to expose every cell to a lethal dose. This screening effect was interestingly shown in a patient who had a massive inoperable growth with discoloured bosses on the skin surface (No. 14). After two radium treatments the bosses had disappeared and the whole tumour was greatly reduced in size. There was, however, a residual mass after nine months which I thought it was wise to excise. Cross-sections through the specimen showed that it consisted almost entirely of fibrous connective tissue from which all evidence of carcinoma had disappeared, *except* for a few cells immediately under the epidermis. These cells were not normal in appearance and perhaps might have disappeared later; in any case the excision has proved satisfactory, and the patient is quite well after two years and two months. A similar residual lump excised from another patient, one year and four months after radium treatment, was found to consist of fibrous connective tissue only and no trace of carcinoma could be discovered.

Local excision has been called for in comparatively few patients, and the histological evidence is necessarily incomplete. It has, however,

served to demonstrate both the partial and complete destruction of a carcinomatous growth by radium.

### Patients Treated.

When the treatment was still in an experimental stage it was clearly right to treat only those patients who seemed to be unsuitable for operation owing either to the position of the growth or to its being adherent to the chest wall. Later, as confidence in the treatment increased, patients who were suitable for operation were treated with radium, and there has not been any reason to regret this. In judging the results, however, it must be remembered that no selection of favourable cases has been exercised. At first only the most unfavourable cases were chosen and more recently every patient that presented herself has been treated, however advanced the disease appeared to be, provided there were not already demonstrable signs of visceral metastases. On the whole, therefore, the class of patient treated has been very unfavourable as regards prognosis.

### Statistics.

Up to the end of April 1929, 90 patients had been treated, but those treated in 1929 are too recent for statistical consideration and will not be included. This leaves 67 patients, of whom one was a male. Of these 26 have been reckoned »inoperable» and 41 »operable», and it is desirable to consider the results in these two categories separately. The distinction is not always quite a clear one, but it is of much interest to be able to form some idea of what has been done for patients for whom Surgery could have done nothing. The term »apparently cured» has been used with caution; it may be taken to mean that the primary tumour and the axillary glands, if any were detected, have disappeared, and that up to the present time no recurrence has been found or suspected in any other part. One patient, the only male, was apparently cured for 18 months, and then died of intercurrent disease. Under the heading of local improvement are many patients in whom the signs of disease have almost disappeared.

	Operable	Inoperable
Apparently cured . . . . .	12	8
Apparently cured (died from intercurrent disease) . . .	1	
Local improvement . . . . .	20	4
Local improvement (died from metastases) . . . . .	4	9
Local improvement (recurrence in skin or neighbourhood)	3	3
Local improvement (died from other causes) . . . . .	1	2
	<hr/> 41	<hr/> 26

The periods for which the «apparently cured» have been observed are as follows:

	Operable	Inoperable
4 years, 6 months . . . . .	—	1
4 years, 1 month . . . . .	—	1
2 years, 10 months . . . . .	—	1
2 years, 9 months . . . . .	—	1
2 years, 4 months . . . . .	1	1
1 year, 10 months . . . . .	—	1
1 year, 7 months . . . . .	1	—
1 year, 6 months . . . . .	2	1
1 year . . . . .	—	1
9 months . . . . .	2	—
8 months . . . . .	3	—
7 months . . . . .	1	—
6 months . . . . .	2	—
	<hr/> 12	<hr/> 8

It will be seen from the above figures that a good result has been obtained in 45 out of the whole number of 67 patients, and in 12 patients out of 26 whom surgery could not have helped.

#### Advantages of Radium Treatment.

The insertion of radium needles is a trivial operation compared with the radical operation and can always be done under gas and oxygen anaesthesia. The mortality rate is nil. Furthermore, the areas of lymphatic drainage can be dealt with more effectively with radium than by dissection, as it can be carried as a routine into regions, such as the parasternal and supraclavicular groups of glands, where operation usually cannot reach. Radium can be applied to almost any case, and surprising results can be obtained in many patients who would be unsuitable for any operation. In those cases which are «operable» effects will follow which for permanence seem to be not inferior to the results of operation, and the patients are unmutilated. Personal experience of both methods of treatment over a period of years has convinced me that radium is on the whole to be preferred to operation, and that the patient's interests will be best served by further development of technique and careful observation of results.

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## SUMMARY

The author during the last five years has come to regard treatment of primary carcinoma of the breast with radium needles as preferable to operation. A total of 90 patients has been treated from Aug. 1924 to April, 1929, many of these having operable tumours.

The dosage employed is relatively small (up to 100 mgr.), and the time of exposure long (7 days or more).

The radium is distributed in two main areas (1) the primary growth, (2) the lymphatic drainage, including the pectoral area, axilla, infraclavicular, supraclavicular, intercostal spaces.

The needles are inserted through small stab wounds under gas- and -oxygen anaesthesia.

The effect on the primary growth is usually complete after four months have elapsed; if it has not completely disappeared after this time, further treatment, operation or radiological, may have to be considered. No extensive operation is ever needed. Usually no operation is performed. Enlarged lymph glands respond well to radium and usually disappear.

A histological proof of the nature of the growth was obtained in the first fifty cases, but no specimen is now taken as it has been found that cutting into the tumour sometimes results in the appearance of an implantation growth.

Some histological evidence of the effect of radium on the tumours has been obtained.

Of the 90 patients treated, 23 are recent; of the remaining 67, 41 have been operable, and 26 inoperable. A good result has been obtained in 45 of these 67, 12 of the 45 being inoperable. Patients have remained »apparently cured» up to  $4\frac{1}{2}$  years after treatment.

## ZUSAMMENFASSUNG

Verf. ist in den letzten 5 Jahren zu der Ansicht gekommen, dass die Behandlung des primären Mammakarzinoms mit Radiumnadeln einer Operation vorzuziehen ist. In der Zeit vom Aug. 1924 bis April 1929 wurden im ganzen 90 Patienten behandelt, von welchen viele operable Tumoren hatten.

Die angewendete Dosis ist relativ klein (bis 100 mg), und die Expositionszeit lang (7 Tage oder länger).

Das Radium wird auf zwei Hauptgebiete verteilt 1) die primäre Geschwulst, 2) die Lymphwege einschliesslich des pektoralen Gebietes, der Axilla, der Reg. infraclavicular, supraclavicular, und der Interkostalräume.

Die Nadeln werden durch kleine Stichwunden unter Lachgas-Sauerstoff-Anästhesie eingeführt.

Die Einwirkung auf das primäre Karzinom ist gewöhnlich nach Ablauf von 4 Monaten vollständig erreicht; wenn die Geschwulst nach dieser Zeit nicht gänzlich verschwunden ist, dürfte eine weitere entweder operative oder radiologische Behandlung zu erwägen sein. Eine eingreifende Operation ist niemals erforderlich. Im allgemeinen braucht überhaupt keine Operation ausgeführt zu werden. Vergrösserte Lymphdrüsen reagieren gut auf Radium und verschwinden gewöhnlich.

In den ersten 50 Fällen wurde eine Probeexzision zur histologischen Untersuchung der Natur der Geschwulst gemacht, jetzt werden aber keine Proben mehr entnommen, weil sich gezeigt hat, dass Inzision in den Tumor mitunter das Auftreten einer Implantationsgeschwulst zur Folge hat.

Mehrfach wurden histologische Beweise für die Wirkung des Radiums auf die Tumoren erhalten.

Von den 90 behandelten Patienten waren 23 frühe Fälle; von den übrigen 67 waren 41 operabel, 26 inoperabel. In 45 von diesen 67 Fällen wurde ein gutes Resultat erhalten, 12 von diesen 45 Fällen waren inoperabel. Die Patienten blieben bis zu 4½ Jahren nach der Behandlung »anscheinend geheilt».

## RÉSUMÉ

L'auteur a été amené, au cours de ces cinq dernières années, à considérer le traitement du cancer primaire du sein par les aiguilles de radium comme préférable au traitement opératoire. D'août 1924 à avril 1929, il a traité 90 malades, dont plusieurs présentaient des tumeurs parfaitement opérables.

Les doses utilisées sont relativement faibles (100 mg. au plus) et les durées d'exposition longues (7 jours ou plus).

Le radium était réparti en deux aires dont la première répond à la tumeur primitive et la seconde aux voies lymphatiques comprenant la région pectorale, l'aisselle et les espaces sous-claviculaires, sus-claviculaires et intercostaux.

Les aiguilles furent placées au moyen de petites incisions profondes pratiquées sous anesthésie au chlorure d'éthyle.

Les effets déterminés sur la tumeur primaire sont généralement complets au bout de 4 mois; si la tumeur n'a pas complètement disparu au bout de ce délai, il y a lieu de songer à un traitement ultérieur, opératoire ou radiologique. Il n'est jamais nécessaire de recourir à une opération étendue, et généralement aucune opération n'a été nécessaire. Les adénites réagissent bien au radium et disparaissent généralement.

Dans les 50 premiers cas, il fut procédé à l'examen histologique de la tumeur primaire; à l'heure actuelle, on ne procède plus au prélèvement d'échantillons: on a constaté en effet que l'excision pratiquée sur la tumeur donne parfois les apparences d'une tumeur d'implantation.

On a réuni certaines preuves histologiques de l'action du radium.

Des 90 cas traités, 23 sont récents; parmi les 67 autres, 41 étaient opérables et 26 inopérables. Le résultat a été favorable dans 45 cas parmi ces 67, 12 sur 45 étant inopérables. Les malades sont restés en état de «guérison apparente» jusqu'à 4 ans et demi après le traitement.



## THE TECHNIQUE OF RADIUM TREATMENT OF CARCINOMA OF THE TONGUE AND MOUTH

by

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In the beginning of the year 1928, the Surgical Professorial Unit of St. Bartholomew's Hospital, encouraged by the results of radium treatment which had been obtained in other regions, decided to study the effect of radium upon carcinomata of the tongue, floor of mouth, palate, lip, and cheek, and an account will be given of the present technique alone.

When the patient is first seen, a careful examination is made, to decide upon the appropriate treatment, and if it is decided to use radium or radon, an estimate is made of the amount which will be needed, so that when the patient is admitted, the necessary dose may await the patient, and not the patient the dose. This plan saves valuable bed space where there is not a constantly available surplus of radium.

In the examination of a growth, careful records are made of its extent, and stamps have been designed for the two lateral aspects and the superior aspect of the tongue and neck, as well as the cross section of the tongue, upon which the extent of the growth can be sketched in each case. A note is made of the distance that the tip of the tongue can be protruded beyond the teeth, this being taken as a valuable indication of the extent of infiltration of the tongue, and a note is made as to whether the growth is fixed to the mandible, or not. A bimanual examination is then made of the floor of the mouth and the base of the tongue, and this often reveals an unexpected extension of the growth. Finally the neck is examined for lymphatic involvement, and it must be remembered that the inferior deep cervical lymph glands may be the seat of secondary deposits, where the more adjacent glands are not enlarged. Occa-

sionally a Wassermann reaction, and subsequent treatment, have confirmed an unexpected diagnosis.

Before operation every effort is made to deal with any sepsis in the mouth. While the radium or radon is in place, any movement of the tongue or cheek is uncomfortable, and food collects in the crevices; this together with any sepsis makes the healthy mucous membrane more susceptible to the effects of irradiation. Dental caries and pyorrhoea therefore receive attention, four-hourly mouth washes are given, and where there are large metal fillings in the teeth, and much radium is to be used, it has been suggested that the fillings should be removed. All these precautions can be taken before admission to the wards.

General or local anaesthesia may be used with equal success; it has been found that endo-tracheal gas, oxygen, and ether, or nasal intubation are most convenient for the surgeon, when a large marine sponge can be placed in the oropharynx at the commencement of the operation. Using local anaesthesia, morphia grains  $\frac{1}{4}$ , and hyoscine hydrochloride grains  $\frac{1}{150}$ , are given one hour before the operation. Fifteen minutes before the operation the local anaesthetic is given, the mouth and pharynx are sprayed with 10 % cocaine, 4 cc. of 2 % novocaine and adrenalin are injected into the inferior dental and lingual nerves, on both sides if necessary; passing the needle alongside the fraenum, and through the substance of the tongue, 5 cc. of this solution are injected into the base of the tongue just in front of the epiglottis. The surgeon can often work with greater ease if 3 cc. of this solution are also injected into the long buccal nerve on the side of the lesion, and atropine grains  $\frac{1}{75}$  given with the morphia ensures a dry field of operation.

At operation the best exposure is obtained with the whole table tilted to an angle of 45 degrees with the feet down, the surgeon standing on the right side and using a head lamp; flat malleable copper retractors and a thick fishing gut suture through the tip of the tongue are helpful.

At the present time it is our practise to treat all primary growths of the buccal cavity by interstitial irradiation; by this method the primary growth can be made to disappear with ease, and it is our experience that this method yields the surest results. For the tongue, floor of the mouth, and palate, radon seeds are used, and for the cheek and lip, radium needles; in all cases a screen of 0.5 mm. of platinum is used, and the period of irradiation varies from six to fourteen days. The seeds used are 1.5 cm. long, and 0.6 cm. in diameter, and their strength varies from 1.0 to 1.5 millicuries, above which the tissues are apt to be burnt; they are placed 1.5 cm. from each other, and at least 1.0 cm. deep to the surface, and are always removed after the requisite dose has been given, without an anaesthetic.

The radium needles used are,

Radium element	Active length	Total length
3.0 mg.	4.8 cm.	6.0 cm.
2.0 mg.	3.2 cm.	4.5 cm.
1.5 mg.	3.0 cm.	4.2 cm.
1.0 mg.	2.0 cm.	3.0 cm.
0.5 mg.	1.0 cm.	1.8 cm.

A platinum-iridium screen is used for the needles to give them greater strength, and they are threaded with medium fishing gut, the ends of which are all tied together, when the needles are inserted, to keep them in place.

The correct dose in any case is decided by experience, and no formula can attempt to take its place, valuable as it may prove to be. The principle which guides us in interstitial irradiation is that it is more important to place the radium all round the growth, rather than inside it; the actively growing edge will then receive a maximum dose, and the centre a summation of the rays from the periphery.

Where the primary tumour is larger than 5 cm., in diameter, it is wise to place a few seeds in the centre of the growth.

During the operation two introducers are used, that one may be loaded while the other is being used, and it is a cardinal rule of irradiation that, during the operation, the surgeon must never take his eyes off the site of irradiation, or he will lose his sense of the disposition of the seeds and needles already inserted.

The following figures are not constant, and serve only to shew minor differences in the treatment of carcinomata of the various sites.

#### *Dorso-anterior region of the tongue:*

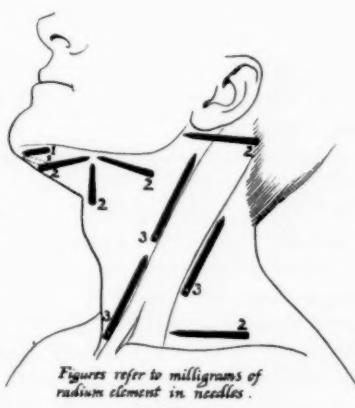
Six to ten seeds of 1.5 millicuries are inserted round the tumour for twelve to fourteen days.

#### *Dorso-posterior region of the tongue:*

Eight to twelve seeds of 1.5 millicuries are inserted round the tumour for twelve to fourteen days, passing the introducer into the tongue alongside the fraenum linguae.

#### *Floor of the mouth:*

Six to eight seeds of 1.0 millicurie are inserted round the tumour for eight to ten days.



*Tonsil:*

Eight to ten seeds of 1.5 millicuries are inserted for ten to twelve days, the outer aspect is irradiated from the neck at the same time, as will be explained later.

*Palate:*

Six to ten seeds of 1.0 millicurie are inserted for eight to ten days.

*Cheek.*

Radium needles are inserted for seven days, often six to seven of 1.0 mg. each.

*Lip.*

Radium needles are inserted for seven days, often five or six of 1.0 mg. each.

In cases of carcinoma of the tongue, floor of the mouth, tonsil, palate, cheek, and lip, we make a rule to treat the glands in the neck in every case, whether these are enlarged or not, treating the glands simultaneously with the primary lesion.

Encouraged by the radium treatment of lymphatic metastases in other sites, and dissatisfied with the results of block dissection, we have tried many methods of irradiating the neck. Our present method, although it may need many alterations in the future, and has not yet stood the test of time, gives the best results in our hands. Stab incisions are made through the skin and deep fascia of the neck, with a number eleven Bard-Parker blade, and radium needles are inserted, always deep to the deep fascia, otherwise the skin will be burnt. There is a standard method of arrangement of the needles which is employed where no enlarged glands can be felt, when there are palpable secondary deposits, this method is modified. The arrangement is,

2 needles of 1 mg. in the submental region.

4 needles of 1 mg. in the submaxillary region.

1 needle of 2 mg. transversely under the upper end of the sternomastoid muscle.

1 needle of 3 mg. along the upper ant. border of sternomastoid.

1 needle of 3 mg. along the lower ant. border of sternomastoid.

1 needle of 3 mg. along the middle of the post. border of this muscle.

1 needle of 3 mg. transversely under the lower border of this muscle.

The needles are threaded with medium fishing gut, and the ends are all tied together, so keeping the needles in place, and preventing any from being lost. Rubber adhesive plaster keeps the dressings in place, and the needles are left *in situ* for from seven to ten days; this gives a dose of from 3,360 to 4,800 mg. hours, or from 25 to 36 m.c.d. to either side of the neck. If secondary deposits can be felt in the neck, this standard arrangement is still adopted, but further radium is massed round the enlarged glands. We rarely insert more than 30 mg. of

the radium element into one side of the neck, our maximum dose being therefore for the ten days, 7,200 mg. hours, or 54 m.c.d. to the one side of the neck.

When the growth involves the tonsil, two or three needles of 2 mg. are inserted from the neck to lie on the outer side of the tonsillar fossa, for the seven days.

When the glands in the neck are fixed to the mandible, and in some cases when they are fixed to the skin, the neck is first irradiated by means of a Columbia paste collar, 15 mm. thick for 14 days; up to 50 mg. of radium element are used on either side, and 0.5 mm. thickness of platinum screening is best. Subsequently the glands may become smaller, and allow of an easier insertion of the radium needles according to the usual method, as it is felt that surface irradiation alone is insufficient; a period of one month is allowed to elapse between the first and second irradiation of the neck, and the primary growth is treated at the time of the first irradiation.

Using these methods no case of radium necrosis of the mandible has occurred.

It is essential, if the best results are to be obtained with radium, that all cases should be systematically followed up. It is our custom to see these cases weekly for the first month, fortnightly for the next two months, monthly for the next six months, and two monthly until two years after irradiation, then they go on to the permanent three monthly follow-up list. It is important to be able to say at the earliest possible moment, whether the total dose has been sufficient or not, and we think that it should be possible to form a definite opinion in from eight to ten weeks, and if by this time there is any doubt about the effect of the first dose, a second course of treatment should be immediately carried out. It appears to us that a previous irradiation makes no difference to the response to a second dose.

In all cases where the Wassermann reaction is positive, anti-syphilitic treatment is carried out from the first. Our only contra-indications are metastases beyond the neck, e. g., in the mediastinum; extensive metastases in the inferior deep cervical lymph glands; and very massive primary growths, continuous with metastases in the neck.

## SUMMARY

The methods of examination of the patient, and of estimation of the dosage of radium are detailed, and emphasis is laid on the necessity for the elimination of oral sepsis. The methods of anaesthesia, general and local, are described.

The primary growth is usually treated by interstitial irradiation with radium needles or radon seeds, the period varying from six to fourteen days.

The glandular areas are treated with radium needles according to a standardised arrangement, covering the submental, submaxillary, and sterno-mastoid regions. The needles are left in position for seven to ten days. When the glands are large they are first irradiated by an external radium collar of «Columbia paste».

The patients are systematically watched, and a second treatment is given as soon as it becomes apparent that the first has been inadequate. Anti-syphilitic treatment is given whenever the Wassermann reaction is positive.

(No statistics are given, the treatment having been systematised only in 1928.)

## ZUSAMMENFASSUNG

Die Abhandlung berichtet im Detail über die Methoden für die Untersuchung des Patienten sowie über die Abschätzung der Radiumdosierung und beschreibt die Methoden der allgemeinen wie der lokalen Anästhesie. Auf die Notwendigkeit der Eliminierung oraler Sepsis wird besonderes Gewicht gelegt.

Die Behandlung der primären Geschwulst besteht gewöhnlich in interstitieller Bestrahlung mit Radiumnadeln oder Radonseeds durch variierend lange Zeit zwischen 6—14 Tagen.

Die Drüsenregionen werden nach einer standardisierten Anordnung mit Radiumnadeln behandelt, derart, dass die submentale, die submaxillare und die Sternomastoidalregion gedeckt sind. Die Nadeln bleiben 7—10 Tage liegen. Wenn die Drüsen gross sind, werden sie zuerst mit einer äusserlichen Applikation von Radium mittels eines Kragens aus «Columbiapaste» behandelt.

Die Patienten werden systematisch beobachtet, und, sobald sich herausstellt, dass die erste Behandlung unzureichend war, wird eine zweite gegeben. Wenn die Wassermannsche Reaktion positiv ist, wird der Patient immer einer antisyphilitischen Behandlung unterzogen.

(Eine Statistik ist nicht mitgeteilt, weil die Behandlung erst im Jahre 1928 systematisiert wurde.)

## RÉSUMÉ

Description détaillée des méthodes d'examen du malade, de l'appréciation des doses nécessaires, en insistant sur la nécessité d'éliminer toute infection buccale. Exposition des méthodes d'anesthésie générale ou locale.

La tumeur primaire est généralement traitée par une irradiation interstitielle à l'aide d'aiguilles de radium ou de «radon seeds», pendant une période variant entre six et quatorze jours.

Les zones ganglionnaires sont traitées par des aiguilles de radium, combinées avec un dispositif spécial couvrant les régions sous-mentale, sous-maxillaire et sterno-mastoidienne. Les aiguilles sont laissées en place de sept à dix jours. Lorsqu'il existe de l'hypertrophie ganglionnaire, la région est d'abord irradiée au moyen d'un col de radium en «spâte de Colombie».

Les malades sont l'objet d'une surveillance systématique et un second traitement est administré dès qu'on s'aperçoit que le premier n'a pas été suffisant. Le traitement spécifique est institué lorsque le Wassermann est positif.

(Aucune statistique n'est communiquée, le traitement n'étant appliqué d'une façon systématique que depuis 1928.)



## X-RAYS IN THE TREATMENT OF MALIGNANT DISEASE

by

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It is now over 25 years since X-rays were first used in the treatment of malignant disease and over 10 since WINTZ first announced a scientific and accurate method of deep X-ray therapy: yet even those radiologists who have practised X-ray therapy are still very far from agreement as to its value, and the methods and wave-lengths which should be used. Small wonder is it then, that this method of treatment is regarded with something approaching suspicion by the general body of the Medical Profession.

At. St. Bartholomew's Hospital results have been obtained during the past four and a half years which make it clear that X-ray therapy has a definite value in the treatment of malignant disease and it appears that much of the criticism which has been levelled against X-rays has not been justified.

It may clear the air somewhat if we begin by discussing the reasons for this state of affairs. In the first place, we must recognize the fact that while the skill of the radiologist is of very great importance in determining the quality of the results, it is by no means the only important factor. The technique is at least equally important. It is in the great diversity of techniques which have been employed by different radiologists that the reason lies for the lack of uniformity in the results which have been obtained. For this, however, no blame can attach to the radiologist, since very little knowledge has hitherto been available which

would help him to choose among the multitude of possible permutations and combinations of the factors in the treatment. Thus, many different wave-lengths and mixtures of wave-lengths have been used: the dose may be given in one intensive application or may be fractionated: when so divided, the fractions may be equal or unequal and may be given at varying intervals. All these things had to be investigated and many still remain to be tried.

In this respect there is a fundamental difference between X-ray therapy and, say, surgery. While the variety of methods of treatment of a carcinoma of the breast, for instance by X-rays, is very great, surgical technique does not permit of any number of great and fundamental variations. We can thus say from our experience of the surgical treatment of the condition, that surgery in competent hands is of a certain value in the treatment of carcinoma of the breast. As regards X-ray therapy, however, all that we can say is that *when a specified technique is used* X-rays have a certain value in the treatment of the condition.

It is very important that these facts should be realised, since the sweeping condemnatory statements that one frequently sees made on very insufficient evidence, can only serve to retard the progress of a science which is pregnant with possibilities for the relief of human suffering.

Another factor is that when this work was begun, practically every case submitted for X-ray treatment was not only inoperable but extremely advanced. Obviously only a small percentage of cures will be obtained in such cases, so that everyone must see several relative failures for each success. There was therefore a tendency to be discouraged if the earlier cases seen were failures.

With a full appreciation of these difficulties, the Medical Council of St. Bartholomew's Hospital decided, in 1922, to institute an investigation into the results of the treatment of malignant disease by deep X-ray therapy.

With the generous financial assistance of the British Empire Cancer Campaign a special department, the Radiotherapeutic Research Department, was created for the treatment of these cases under strict research conditions. This Department began work in 1924.

It was decided at the outset, in order to prevent overcrowding of the Department with work, to limit the investigation to five groups of cases, namely malignant disease of the upper air passages, breast, uterus, rectum and oesophagus.

The present article is a brief review of the work of the Radiotherapeutic Research Department and the results obtained in it.

### Selection of Cases

A member of the Staff of the Hospital was appointed in charge of each of the groups of cases above enumerated, by whom, in consultation with the writers, the cases were selected.

As a rule, patients with generalized deposits and patients who were obviously moribund were excluded. There were, however, a few exceptions to this rule which will be noted in the proper place.

Except a few cases in the uterus group, all the cases treated were technically inoperable. Moreover, most of the cases, in which the disease was sufficiently localized for radium treatment, were treated by radium, thus leaving only the more advanced inoperable cases for the X-ray treatment.

### Technique

X-rays of the shortest obtainable wave-length were used. The maximum secondary voltage on the tube was 185 kilovolts until June 1926, and after that 196 kilovolts. This was spectrographically determined. Great difficulty was experienced in obtaining tubes capable of withstanding the latter voltage.

The filtration was, prior to June 1926, 0.5 mm. zinc and after that date 1.5 mm. copper.

The results have definitely improved since the change over to the higher voltage and filtration, at any rate in the upper air passages and uterus groups.

Since November 1925, constant high tension has been in use, thus raising the average voltage. Though evidence that better results have been obtained since this date is not definite, we both incline to the view that this is the case.

A moderate erythema was taken as the unit of dosage. This erythema has a latent period of 12 to 21 days and 80 % of it will just produce a faint erythema followed by well-marked pigmentation in most cases. It is equal to 230e (Friedreich) under the conditions at present in use (196 K. V. and 1.5 mm. copper).

Two hundred and fifty-five cases were treated from the commencement of the research to December 31st, 1928. Of these the first 30 were treated by intensive methods, according to the principles first enunciated by Professor WINTZ of Erlangen for the treatment of carcinoma of the uterus. In these cases the aim was to secure a dose of 90—110 % of the erythema dose throughout the region involved in the disease, the treatment being completed in one or at most two days.

The remaining 225 cases were treated by intensive split-dose methods, in which the dose was applied in daily fractions on consecutive days, totalling up to the maximum possible dose which could be borne without unduly damaging healthy tissues.

It was found, for instance, that 2.2 erythema doses could be borne by the skin when this dose was applied in twelve approximately equal fractions administered over a period of a fortnight. The period over which the treatment was spread in the cases treated by intensive split-dose methods varied from nine to eighteen days.

In all the cases treated, by either method, it was attempted to distribute the dose as homogeneously as possible throughout the region involved in the disease. The fractions of the dose were as nearly equal as possible.

At the end of the first year's work, it was observed that the results which were being obtained by the split-dose methods were greatly superior to those which were being obtained by the single-dose method. Moreover the disturbance of the patient's health was much less severe and the method was much less dangerous. Accordingly it was decided to treat a large number of cases in this way.

It should be said, that, at the time that these observations were made, the cases which were being sent for treatment were principally carcinomata in the upper air passage and uterus groups, and that it was in these cases that the superiority of the split-dose methods over the single-dose methods was evident. Further experience in the treatment of malignant disease of the upper air passages and uterus has confirmed the value of this technique in the treatment of these conditions. In malignant disease of the oesophagus, rectum and breast, however, we have not been able to confirm the superiority of divided doses, nor can we claim to have given the intensive single-dose method a fair trial as yet. There is, indeed, no reason why a technique which has given unsatisfactory results in one type of carcinoma should not be applied successfully to the treatment of another type of the disease, and vice versa.

In certain cases in the upper air passage, uterus, breast and rectum groups, in addition to the X-ray treatment, radium was applied.

Certain special problems in connection with combined X-ray and radium treatment are discussed in another paper in this issue, and much of what has been said there concerning sequence and interval in combined treatments applies equally here. It is felt, however, that nothing would be gained at this juncture by further sub-dividing the already small number of cases treated by combined methods in the upper air passage and breast groups, into five sub-groups, as has been done in the uterus group.

The radium technique in the combined treatment has been the same as that employed in the non-combined treatments and described in other papers in this number.

As regards dosage, no reduction of dosage either of X-rays or of radium was found to be necessary in the case of the upper air passage and uterus groups: in these cases the radium was not applied to the skin surface. In the breast group, however, a severe burn of the skin was produced in one case when radium needles were buried and full dosage given after all signs of reaction from an intensive X-ray treatment had subsided. In two other cases, in which the X-rays were applied after the radium, several very small but very painful skin burns were produced at the sites of insertion of the radium needles. These facts suggests that one ought to proceed with caution as regards dosage when carrying out combined treatments in this region, or indeed in any situation where the radium needles cannot be inserted at a sufficient depth below the skin.

In addition to the 255 cases treated by the above methods, a small series of cases was treated in collaboration with the Lead Research Department by X-rays after injection with colloidal lead. These cases do not come within the scope of this paper and will not be referred to further here.

## Results

### A. General observations

It was found that apart from the extent of the disease, certain circumstances of a more general character exercised an effect on the result of the treatment. Thus, the proportion of destitute patients among those who had done well was almost negligible, while the proportion of such patients among the remainder was quite considerable, suggesting that poor conditions of life are a powerful adverse influence on the course of the disease subsequent to treatment.

The influence of alcohol may also be referred to here. Alcoholic patients are very bad subjects for X-ray treatment; they tend to get excessive reactions, and their growths tend to be radio-resistant.

As regards the influence of age, several patients treated were over 80 years of age. These patients stand X-ray treatment very well, but the disease is usually of a slow-growing type, and therefore does not respond well to X-ray treatment.

The general condition of the patient is of little value as a guide to the prognosis with X-ray treatment. It is frequently found that in strong healthy-looking patients the disease is uninfluenced by treatment, while patients in whom cachexia has already set in sometimes do well.

**B. Local conditions having an influence on the result**

Of local conditions having an influence upon the result, apart from the extent of the disease, the most important is sepsis. Septic growths should never be treated except in the presence of free drainage. Even when the latter has been established, full dosage should not be applied at first. Much improvement can frequently be wrought in the sepsis by the application of small doses, of the order of one fifth of an erythema dose, two or three times over about a week. Thereafter fractionated intensive treatment can be applied with full dosage.

**C. General effects of treatment**

X-ray sickness, which was almost constant in occurrence with the intensive single-dose methods, has been seen only very occasionally since the introduction of the intensive split-dose technique. With the latter technique, languor and tiredness are usually complained of towards the end of the treatment. These usually pass off during about three weeks.

A considerable amount of weight is usually lost during the treatment and for two or three weeks afterwards. Thereafter weight is regained, and the final weight is frequently considerably above the normal weight for the patient. Coincidently with the gain in weight, in the great majority of patients, a remarkable improvement in the general condition is observed, and this improvement is seen even in cases in which the local disease seems to be little influenced by treatment.

**D. Local effects**

*Pain.* Some relief from pain was almost constantly produced as a result of the treatment, and frequently this relief was complete. Pain was least influenced in those cases in which it was due to involvement of nerves in masses of carcinomatous glands in the neck secondary to disease in the upper air passages.

*Haemorrhage.* It was found, that haemorrhage, when not actually of arterial origin, was almost invariably relieved. In many cases, however, this relief was only temporary, the haemorrhage recurring with the further progress of the disease.

*Effect on Ulceration.* Except in the case of fungating secondary glands in the neck, it was found that ulceration was almost invariably reduced in size and frequently completely healed as a result of the X-ray treatment. This healing was, however, frequently only temporary, the ulceration recurring if the disease advanced.

In the upper air passage and uterus groups nearly half the patients treated became completely free from all symptoms and signs of the

disease after the treatment. Of these cases, rather more than half recurred; the interval during which they remained free from signs of the disease before recurrence varied considerably. It averaged about six months.

### Numerical Results

#### 1. Upper Air Passage Group

A general view of the results obtained in this group is given in the following table.

*Note.* The letters N A D (nothing abnormal demonstrated) mean that the patient is alive, well, and free from evidence of the disease at the time of writing (May 1929).

	1924-25	1926	1927	1928	Total
Number treated . . . . .	20	37	26	43	126
Now N A D . . . . .	3	6	6	9	24
N A D, then recurrence . . . . .	6	11	8	14	39
Alive, disease present . . . . .	1	2	2	26	31
Dead . . . . .	16	29	18	8	71

Separating the cases in which X-rays only, and X-rays combined with radium, were applied, the results were as follows.

#### Upper Air Passage Group Cases treated by X-rays only

	1924-25	1926	1927	1928	Total
Number treated . . . . .	14	32	18	33	97
Now N A D . . . . .	1	5	5	8	19
Alive, disease present . . . . .	0	2	2	20	24
Dead . . . . .	13	25	11	5	54

#### Cases treated by X-rays in Combination with Radium

	1924-25	1926	1927	1928	Total
Number treated . . . . .	6	5	8	10	29
Now N A D . . . . .	2	1	1	1	5
Alive, disease present . . . . .	1	0	0	6	7
Dead . . . . .	3	4	7	3	17

A more detailed classification of the cases in the upper air passage group and of the results obtained is given in the following table.

*Explanation of abbreviations used in table*

Ep = squamous-celled epithelioma. End = endothelioma.  
 Sa = sarcoma. Rec = recurrence after operation.  
 Glands+ = enlarged lymphatic glands present in neck at time of treatment.  
 Numbers in brackets refer to cases in which the clinical diagnosis was not confirmed microscopically. Clinically the diagnoses were not in doubt.  
 Example — 4(1) means 4 cases in 1 of which the clinical diagnosis was not confirmed microscopically.  
 >under 1 yr, over 1 yr etc. refer to the time which elapsed after treatment.

**Classification of Cases and Results, Upper Air Passage Group**

	No. tr.	Alive and NAD May 1929					Alive, disease pre- sent May 1929					Dead lived for		
		under 1 yr	over 1 yr	over 2 yrs	over 3 yrs	over 4 yrs	under 1 yr	over 1 yr	over 2 yrs	over 3 yrs	under 1 yr	over 1 yr	over 2 yrs	
Ep lip ree. glands+	1	0	0	0	0	0	0	0	0	0	1	0	0	
Ep cheek, inner surface	1	0	1	0	0	0	0	0	0	0	0	0	0	
Ep floor of mouth glands+	5	0	0	0	0	0	1	1	0	0	2	1	0	
Ep upr jaw	8(3)	0	0	0	0	0	3	1	0	0	3(2)	1(1)	0	
Ep tongue glands+	4	0	0	0	1	0	0	0	0	1	1	0	1	
Sa upr jaw	8(3)	0	0	1	0	0	2(1)	1	0	0	3(2)	1	0	
Rec. glands from Ep of tongue	8	0	0	1	0	0	2	0	0	0	4	1	0	
End tonsil glands+	2	0	0	1	1	0	0	0	0	0	0	0	0	
Ep palatal glands+	4	0	1	1	0	0	0	0	0	0	1	1	0	
Myeloma palate glands+	1	0	0	0	1	0	0	0	0	0	0	0	0	
Ep tonsillar region glands+	21	2	0	0	0	0	3	1	0	0	8	7	0	
Ep tonsillar region no glands	2(1)	0	0	0	0	1(1)	1	0	0	0	0	0	0	
Sa tonsil glands+ neck and mediastinum	1	0	0	0	1	0	0	0	0	0	0	0	0	
End pharynx glands+	3	0	0	1	0	0	0	0	0	0	0	2	0	
Sa pharynx glands+	6(1)	1(1)	1	1	0	0	1	0	0	0	2	0	0	
Ep pharynx glands+	2	0	1	0	0	0	0	0	0	0	1	0	0	
Ep larynx intrinsic	2	0	0	0	1	0	0	0	0	0	1	0	0	
Ep larynx extr. glands+	32	1	2	0	0	0	10	2	0	0	11	5	1	
Ep larynx post cricoid	7(1)	0	0	0	0	0	0	0	0	0	5(1)	2	0	
Ep glands no primary found	7	0	0	1	0	0	0	0	0	0	4	2	0	
Sa glands neck	1(1)	1(1)	0	0	0	0	0	0	0	0	0	0	0	

**2. Breast Group**

All the cases in this group were carcinomata, and all were microscopically confirmed.

A general view of the results obtained is given under.

	Treated 1924—25	Treated 1926	Treated 1927	Treated 1928	Total
Number treated . . . . .	9	10	10	11	40
Now N A D . . . . .	0	2	0	1	3
N A D, then recurrence . . . . .	1	4	1	0	6
Little or no improvement . . . . .	8	4	9	9	30
Alive, disease present . . . . .	1	3	1	6	11
Dead . . . . .	8	5	9	4	26

A more detailed classification of the cases and the results obtained is given below.

(For explanation of abbreviations used see page 416.)

#### Classification of Cases and Results, Breast Group

No. tr.		Alive and N A D May 1929				Alive, disease pre- sent May 1929				Dead lived for		
		under 1 yr	over 1 yr	over 2 yrs	over 3 yrs	under 1 yr	over 1 yr	over 2 yrs	over 3 yrs	under 1 yr	over 1 yr	over 2 yrs
Cr breast primary . . . . .	17	0	0	1	1	3	2	1	1	5	1	2
Cr breast primary with supra- clavie. and axillary glands +	7	0	0	0	0	1	1	0	0	3	1	1
Cr breast primary mediastinal glands + . . . . .	2	0	0	0	0	1	0	0	0	0	1	0
Cr breast primary supraclavie. and mediastinal glands + . . . . .	3	0	0	0	0	1	0	0	0	1	1	0
Cr breast rec. post op. supra- clavie. glands + . . . . .	3	0	0	0	0	0	0	0	0	1	2	0
Cr breast rec. supraclavie. and mediastinal glands + . . . . .	8	1	0	0	0	0	0	0	0	5	2	0

#### 3. Uterus Group

The cases in this group are dealt with elsewhere in this issue, and need not further be referred to here.

#### 4. Rectum Group

In five out of the twenty-two cases treated in this group, the clinical diagnosis was not confirmed by microscopical examination. In one of the unconfirmed cases a complete disappearance of all signs and symptoms of the disease followed the treatment. Doubt is now felt as to whether this case really was a carcinoma, and it has accordingly been eliminated from the statistic.

The remaining twenty-one cases are classified and the results set forth below.

(For explanation of abbreviations used in table see page 416.)

	No. tr.	Alive N A D may 1929	Alive, disease present			Dead lived for		
			under 1 yr	over 1 yr	over 2 yrs	under 1 yr	over 1 yr	over 2 yrs
Cr rectum primary . . . . .	12	0	1	0	0	7	4	0
Cr rectum rec. post-op. . . . .	8	0	0	2	1	3	2	0
Sa rectum . . . . .	1	0	0	0	0	0	1	0

### 5. Oesophagus Group

In only two out of a total of nine cases treated was the removal of a piece of the growth for microscopical examination considered justifiable. The subsequent course of the disease, however, has in no case left room for doubt as to the diagnosis.

Of the nine cases, only two are alive. Of the two who are alive, one is well and has gained considerably in weight, fifteen months after treatment. A recurrence has recently appeared in this case. The other is now dying, nine months after treatment.

Of the seven patients who are dead, only one lived for more than a year.

We have attempted in the foregoing to summarize briefly the results which have been obtained during the past four and a half years in the Radiotherapeutic Research Department at St. Bartholomew's Hospital. Space does not permit of a more complete account of these results here, but it is proposed to publish a detailed report early in 1929.

While it is impossible after only four and a half years work to form any rigid conclusions as to the value of X-rays in the treatment of malignant disease, certain conclusions of a more general character do emerge from the observations herein recorded.

In the first place, it is clear that a considerable amelioration of suffering may be effected by the use of X-rays, and this with very little risk and at the expense of but little discomfort to the patients. Secondly, it has been seen that when the disease affects certain regions a considerable proportion of cases, even of advanced cases, may be rendered free from all signs and symptoms of the disease for a longer or shorter period. Whether some of these patients will remain free from the disease permanently, remains to be seen. That they may do so for upwards of four years is already obvious.

Finally it has been seen that little benefit has resulted from the treatment in the cases in the rectum and oesophagus groups. Whether these cases which have proved refractory to the techniques which have been used up to the present will respond to other techniques which may be devised, is one of the problems which will have to be investigated in the future.

## SUMMARY

Certain factors having an influence upon the results of Deep X-Ray Therapy in malignant disease are discussed. The results reported in the literature by different authorities have varied greatly. As a probable explanation for these wide variations attention is called to the great number of variable factors in X-ray therapeutic technique, and the almost complete lack of any knowledge hitherto which would serve as a guide in choosing between the possible variations. (E.g. variation in quality of ray, in filtration, in the intensity and time factors etc.) The result has been the development of a very great number of different techniques for the treatment of each condition, and a complete lack of uniformity in the practices of different clinics.

The technique employed and the results obtained during the past 4½ years in the Radiotherapeutic Research Department of St. Bartholomew's Hospital are briefly described.

Very encouraging results have been obtained in malignant disease in the upper air passages and uterus but not in the rectum, oesophagus and breast, although similar techniques were used in all cases.

It is suggested that different techniques may be required in different types of malignant disease and reference is made in this connection to the possible variation in the threshold intensity for different types of epithelium.

It is concluded that complete disappearance of a malignant growth (whether carcinoma or sarcoma) may in certain cases be effected by X-ray treatment. This apparent cure may last for several years. It is not yet possible to say if it may be permanent.

## ZUSAMMENFASSUNG

Die Verf. erörtern gewisse Faktoren, die auf die Resultate von Röntgen-Tiefentherapie bei malignen Krankheiten von Einfluss sind. Die von verschiedenen Autoren in der Literatur berichteten Resultate waren sehr verschieden. Was die wahrscheinliche Erklärung dieser grossen Variationen betrifft, machen die Verff. auf die grosse Zahl von variablen Faktoren in der therapeutischen Röntgentechnik aufmerksam und auf den bisher fast vollständigen Mangel an Kenntnissen darüber, die als Leitschnur für die Wahl zwischen den möglichen Variationen dienen könnten (z. B. Variation der Strahlenqualität, des Filters, der Dosierung und der Zeitfaktoren etc.). Das Resultat war die Entwicklung einer sehr grossen Zahl von verschiedenen Techniken für die Behandlung jedes Zustandes und ein vollständiges Fehlen von Einheitlichkeit in der Praxis verschiedener Kliniken.

Hieran schliesst sich eine kurze Beschreibung der in den letzten 4½ Jahren in der Radiotherapeutischen Forschungsabteilung des St. Bartholomew's Hospital angewandten Technik und der erzielten Resultate.

Bei malignen Leiden der oberen Luftwege und des Uterus wurden sehr ermutigende Resultate erhalten, nicht aber bei Krankheiten des Rektums, des Ösophagus und der Brust, obgleich in allen Fällen dieselbe Technik verwendet wurde. Die Verff. sprechen die Vermutung aus, dass für die verschiedenen Typen von malignen Leiden verschiedene Technik erforderlich sein mag und verweisen in diesem Zusammenhang auf die mögliche Variation in der Schwellendosis für verschiedene Typen von Epithel.

## RÉSUMÉ

Les auteurs discutent certains facteurs pouvant influer sur les résultats de la radiothérapie profonde dans les affections malignes. Les résultats communiqués dans la littérature par diverses autorités diffèrent grandement. Ces différences s'expliquent probablement par le grand nombre de facteurs variables que comporte la technique de la radiothérapie et par l'absence à peu près complète de toutes connaissances pouvant permettre de choisir entre les variations possibles (variations de qualité des rayons, variations de filtration, d'intensité, de durée, etc.). Il en est résulté un nombre considérable de techniques différentes pour le traitement de chaque cas et une absence complète d'uniformité dans la pratique des différentes cliniques.

Les auteurs décrivent brièvement la technique utilisée et les résultats obtenus au cours des  $4\frac{1}{2}$  dernières années dans le service des recherches radiothérapeutiques du St Batholomew's Hospital.

On a obtenu des résultats très encourageants dans le traitement des affections malignes des voies respiratoires supérieures et de l'utérus, mais non dans les affections malignes du rectum, de l'œsophage et du sein, bien qu'on ait recouru, dans l'ensemble de ces cas, à des techniques analogues.

Les auteurs estiment qu'il y aurait peut-être lieu d'appliquer des techniques différentes aux différents types d'affections malignes et suggèrent à ce propos la possibilité de faire varier les intensités de début suivant les divers types d'épitheliums.

